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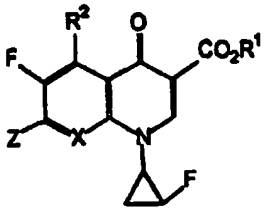
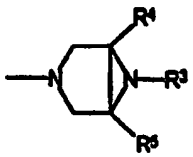


(I)



(α)

(57) Abstract

The present invention relates to a novel quinoline compound represented by general formula (I) and its pharmaceutically acceptable salt, which shows a superior antibacterial activity in contrast to the known quinoline based antibacterial agents, wherein R^1 represents hydrogen or ester forming group; R^2 represents hydrogen, amino, lower alkylamino, hydroxy, lower alkoxy, mercapto, lower alkylthio or halogen; Z represents an amine compound having general formula α, (wherein, R^3 represents hydrogen or lower alkyl; R^4 and R^5 are identical to or different from each other, and independently represent hydrogen or C_1-C_2 alkyl); and X represents N or C-R^6 (wherein R^6 represents hydrogen, halogen, hydroxy, methyl, cyano, nitro or methoxy).

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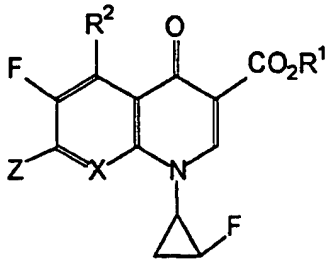
NOVEL QUINOLINE COMPOUND AND PROCESS FOR PREPARATION THEREOF

Background of the Invention

Field of the Invention

The present invention relates to a novel quinoline compound represented by the following general formula (I) which has an excellent antibacterial activity against gram-positive and gram-negative bacteria, particularly methicillin or ofloxacin resistant bacteria and also has a broad antibacterial spectrum and a highly improved pharmacokinetic property :



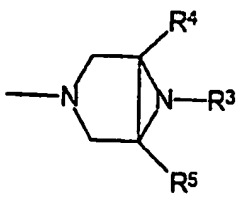
(I)

and its pharmaceutically acceptable salt, in which

R^1 represents hydrogen or ester forming group;

R^2 represents hydrogen, amino, lower alkylamino, hydroxy, lower alkoxy, mercapto, lower alkylthio or halogen;

Z represents an amine compound having the following general formula,



(wherein, R^3 represents hydrogen or lower alkyl; R^4 and R^5 are identical to or different from each other, and independently represent hydrogen or C_1-C_2 alkyl); and

X represents N or C-R^6 (wherein, R^6 represents hydrogen, halogen, hydroxy, methyl, cyano, nitro or methoxy).

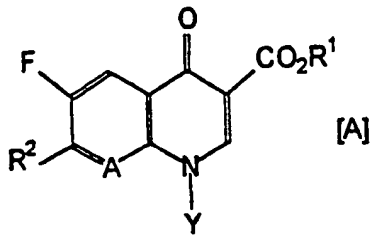
The present invention also relates to a process for preparing the compound of formula (I), as defined above, and to an antibacterial composition comprising the compound of formula (I) as an active ingredient.

Background Art

The previously known quinoline based antibacterial agents, for example norfloxacin, pefloxacin, ofloxacin, ciprofloxacin, sparfloxacin, etc., show an excellent anti bacterial activity against gram-negative bacteria, whereas they have a comparatively low antibacterial activity against gram-positive ones. Especially, these early-stage antibacterial agents bear a problem of developing resistant strains.

Recently, new quinoline based antibacterial agents having various diazabicycloamine substituents on the 7-position of the quinoline nucleus have been developed and reported, and these compounds can be exemplified as follows.

European Patent Application No. 215,650-A_2 discloses a compound of the following general formula [A] :



[A]

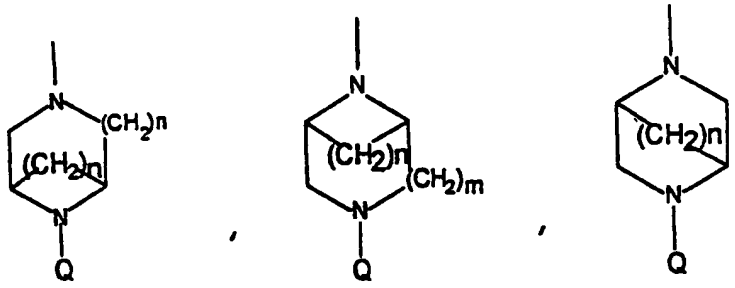
in which,

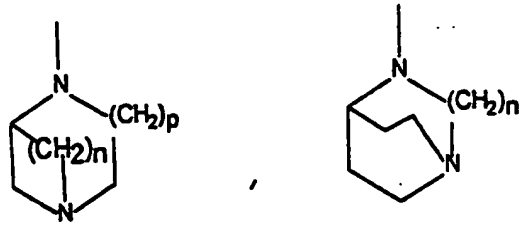
A represents CH, CF, CCl or N;

Y represents C_1-C_3 alkyl, C_1-C_3 haloalkyl, cyclopropyl, vinyl, methoxy, N-methylamino, P-fluorophenyl, P-hydroxyphenyl, P-aminophenyl or, when A is carbon, the A and the nitrogen to which Y is attached can form 5 or 6 membered ring comprising oxygen and substituted by methyl or methylene group;

R^1 represents hydrogen, pharmaceutically acceptable positive ion or C_1-C_6 alkyl; and

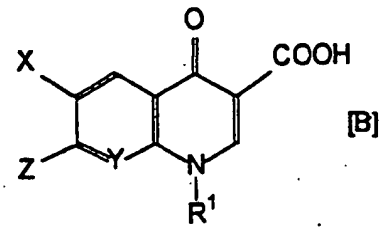
R^2 represents a diazabicycloalkyl group selected from the compounds of the following general formulas :





(wherein, n is an integer of 1 to 3, m is 1 or 2, p is 0 or 1 and Q represents hydrogen or C_1-C_3 alkyl).

European Patent Application No. 266,576-A_2 discloses a compound of the following general formula [B] :

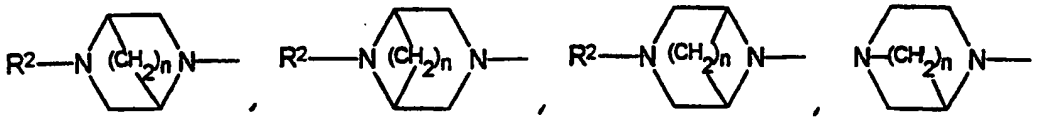


[B]

in which,

R^1 represents substituted or unsubstituted t-alkyl; and

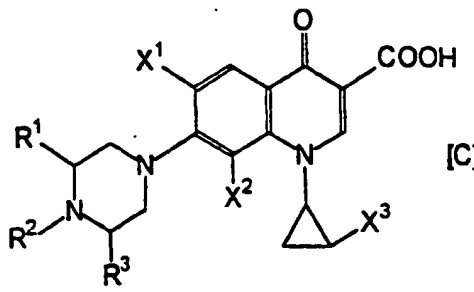
Z represents N-heterocyclic compound selected from the following general formulas :



(wherein, R^2 represents hydrogen or alkyl, n is an integer of 0 to 3).

However, the diazabicycloamine derivatives mentioned above also do not show an improved antimicrobial activity compared with the early-stage antibacterial agents.

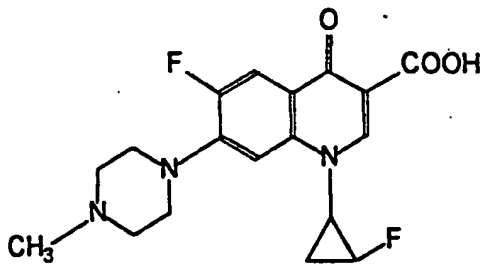
In addition, European Patent Application No. 191,185-A_1 discloses a compound of the following general formula [C] :



[C]

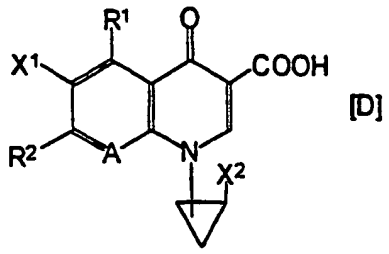
in which,
X^1 and X^2 independently represent hydrogen or halogen;
X^3 represents a halogen;
R^1, R^2 and R^3 represent hydrogen or lower alkyl.

In the above literature, a compound having the following specific formula is mentioned as the most preferable compound among the compounds of the general foumula [C] ;



and it is reported that this compound shows a good pharmacokinetic characteristics due to the appropriate harmonization of aqueous /oily properties, high blood concentration, rapid absorption at the small intestine.

Furthermore, European Patent Application No. 341,493-A_2 discloses a compound of the following general formula [D] :

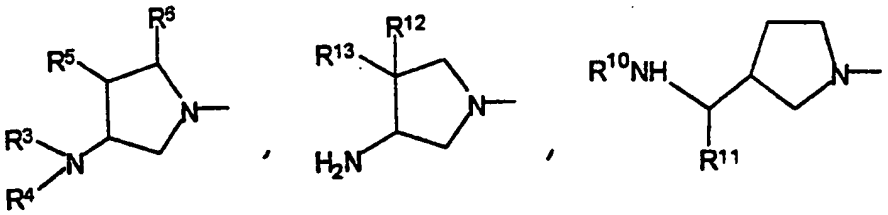


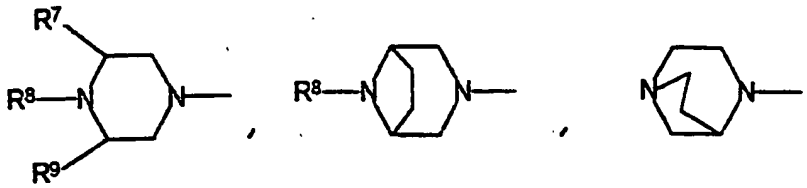
[D]

in which,

X^2 represents a halogen, and

R^2 can be selected from the compounds of the following general formulas :





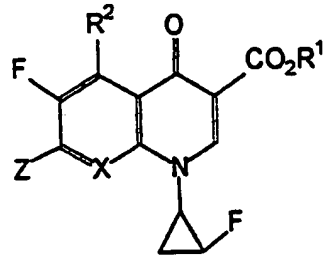
The above compound shows more improved characteristics in view of pharmacokinetic property and toxicity.

Thus, on the basis of prior art as mentioned above the present inventors have extensively studied for a long time to develop a novel antibacterial quinoline compound. As a result, we have identified that a quinolone compound having a fluorocyclopropyl group on N-1 position and a

3,6-diazabicyclo[3.1.0]hexane derivative on C-7 position of the quinoline nucleus can exhibit a potent antibacterial activity against gram-positive and gram-negative strains, particularly Staphylococcus aureus strain as well as highly reduced toxicity in comparison to the prior quinoline based derivatives, and then completed the present invention.

DISCLOSURE OF INVENTION

It is an object of the present invention to provide a novel quinoline compound, especially a compound having a fluorocyclopropyl group on N-1 position and a 3,6-diazabicyclo[3.1.0]hexane derivative on C-7 position of quinoline nucleus represented by the following general formula (I) :



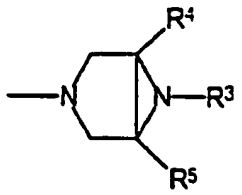
(I)

and its pharmaceutically acceptable non-toxic salt in which,

R^1 represents hydrogen or ester forming group;

R^2 represents hydrogen, amino, lower alkylamino, hydroxy, lower alkoxy, mercapto, lower alkylthio or halogen;

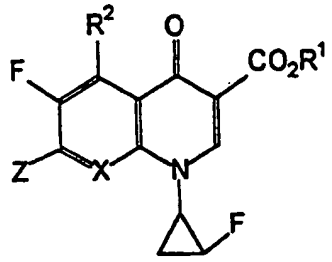
Z represents an amine compound having the following general formula,



(wherein, R^3 represents hydrogen or lower alkyl; R^4 and R^5 are identical to or different from each other, and independently represent hydrogen or C_1-C_2 alkyl); and

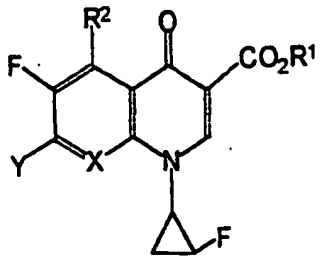
X represents N or C-R^6 (wherein, R^6 represents hydrogen, halogen, hydroxy, methyl, cyano, nitro or methoxy).

It is another object of the present invention to provide a process for preparing the compound of formula (I) :



(I)

and its pharmaceutically acceptable salt, wherein R^1, R^2, Z and X are defined as previously described, characterized in that a 3-quinoline carboxylic acid derivative having the following general formula (II) :



(II)

or a complex compound thereof, wherein R^1, R^2 and X are defined as previously described and Y represents a halogen, is reacted with a 3,6-diazabicyclo[3.1.0]hexane derivative having the following general formula (III) :

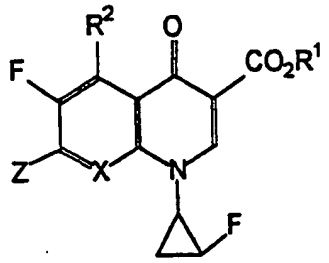
(III)

wherein Z is defined as previously described, in the presence of a base.

It is a further object of the present invention to provide an antibacterial composition comprising a novel quinoline compound of the formula (I) according to the present invention as an active component together with a pharmaceutically acceptable carrier.

BEST MODE FOR CARRYING OUT THE INVENTION

In one aspect, the present invention relates to a novel quinoline compound having the following formula (I) :



(I)

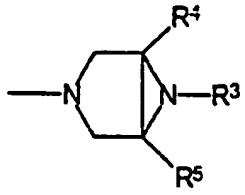
in which,

R^1 represents hydrogen or ester forming group;

R^2 represents hydrogen, amino, lower alkylamino, hydroxy, lower alkoxy, mercapto, lower alkylthio or halogen;

Z represents an amine compound having the following

general formula,



(wherein, R^3 represents hydrogen or lower alkyl; R^4 and R^5 are identical to or different from each other, and independently represent hydrogen or C_1-C_2 alkyl); and

X represents N or C-R^6 (wherein, R^6 represents hydrogen, halogen, hydroxy, methyl, cyano, nitro or methoxy).

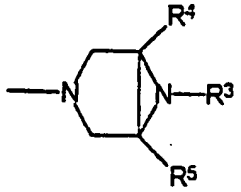
In the definitions for the substituents of the compound of formula (I), the term "lower alkyl" means a straight or branched, saturated hydrocarbon radical having 1 to 4 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, etc.; the terms "lower alkoxy", "lower alkylamino" or "lower alkylthio" mean a form inwhich the lower alkyl group as mentioned above is connected with oxy, amino or thio group respectively; the term "alkenyl" means a straight or branched, unsaturated hydrocarbon radical, for example, ethenyl, propenyl, isopropenyl, etc.; the term "haloalkyl" means an alkyl group substituted with one or more halogen atoms which are identical to or different from each other; and the term "halogen" means fluorine, chlorine, bromine, iodine, etc. In addition, the term "ester forming group" defines all the known ester forming group comprising lower alkyl, cycloalkyl having 3 to 7 carbon atoms and benzyl; and the term "amino protecting group" defines a known amino protecting group such as acyl, alkoxycarbonyl, substituted sulfonyl, substituted or unsubstituted benzyloxycarbonyl, substituted or unsubstituted benzyl, etc.

One preferred group of the novel compound of formula (I) according to the present invention includes the compound, wherein

R^1 represents a hydrogen;

R^2 represents hydrogen or amino;

Z represents an amine compound having the following general formula,



(wherein, R^3 represents hydrogen or lower alkyl; R^4 and R^5 are identical to or different from each other, and independently represent hydrogen or C_1-C_2 alkyl); and

X represents N or C-R^6 (wherein, R^6 represents hydrogen, halogen or methoxy).

Typical examples of the compound of formula (I) provided by the present invention are as follows.

(1) 6,8-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-7-(6-methyl-3,6-diazabicyclo[3.1.0]hexan-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;

(2) 7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6,8-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;

(3) 6,8-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-7-(1-methyl-3,6-diazabicyclo[3.1.0]hexan-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;

(4) 5-amino-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6,8-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;

(5) 8-chloro-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-

7-(1-methyl-3,6-diazabicyclo[3.1.0]hexan-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;
(6) 8-chloro-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;
(7) 8-chloro-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-(cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;
(8) 7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6,8-difluoro-1-(cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;
(9) 7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-(cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;
(10)5-amino-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6,8-difluoro-1-(cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;
(11)7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;
(12)7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and the salt thereof.

Among the compounds of formula (I) defined above, there exist some compounds in their optically active states, especially in the form of pure D isomer, pure L isomer or a mixture thereof, racemate, meso-isomer, dl-isomer, diastereomer mixture, etc. And, an additional asymmetric carbon atom can exist in a substituent such as an alkyl group or in a linking part. Thus, the present invention includes all of those optical isomers of the compound of formula (I) and their mixtures.

The compound of formula (I) according to the present invention can form a pharmaceutically acceptable salt. The "pharmaceutically acceptable salt" herein means a

nontoxic acid-addition salt or a base addition salt which is formed with an alkali metal, an alkaline earth metal or an organic amine.

The aforementioned salt can be prepared in the same reaction system during the final separation or purification step. And it can also be obtained by reacting the compound of formula (I) with an appropriate organic acid, an inorganic acid or a base, respectively, after final separation step.

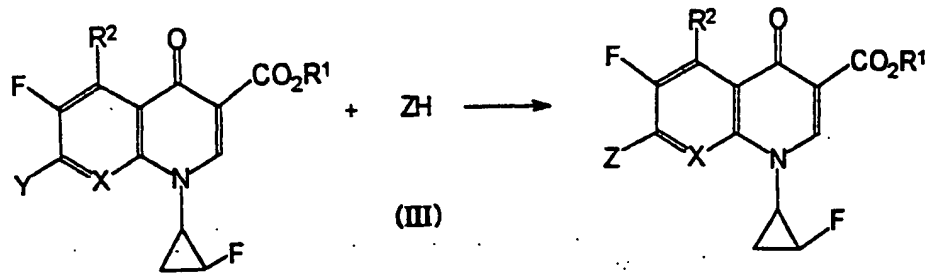
Typical examples of the acid-addition salt as mentioned hereinabove comprise hydrochloride, hydrobromide, sulfate, hydrogen sulfate, formate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, p-toluenesulfonate, methanesulfonate, citrate, maleate, fumarate, succinate, tartarate and ascorbate, more preferably, hydrochloride, lactate and methanesulfonate. Typical examples of the alkali metal and alkaline earth metal salt include sodium, potassium, calcium and magnesium salt. In addition, as appropriate organic amines there may be mentioned N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine, procaine.

Hereinbelow, the present invention will be specifically explained in view of the process for preparing the compound of formula (I) and the pharmaceutical efficacy of that compound.

As shown in the following reaction scheme 1, the compound of formula (I) can be prepared by reacting a 3-quinoline carboxylic acid derivative of the following general formula (II) with a 3,6-diazabicyclo[3.1.0]hexane derivative of the following general formula (III). Therefore, it is another object of the present invention to provide a process for preparing the novel compound of

formula (I) :

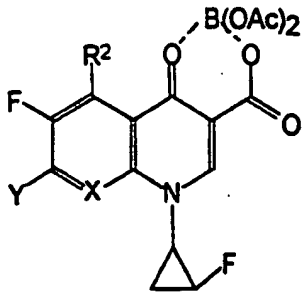
Reaction Scheme 1



(II) (I)

In the above reaction scheme,
R^1, R^2, Z and X are defined as previously described; and
Y represents a halogen.

The compound of formula (I) can be prepared according to the above reaction scheme 1, however if appropriately, it can also be conveniently prepared by reacting a complex compound of the compound of formula (II), preferably a boron complex compound represented by following general formula (II-1), with the compound of formula (III) :



(II-1)

in which,

R^2, X and Y are defined as previously described.

If required, said reaction can be carried out in the absence of any solvent, and of course it can also be practiced in the presence of an appropriate solvent such as tetrahydrofuran, dimethylsulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, acetonitrile, water, alcohol(for example, methanol, ethanol, n-propanol or isopropanol), glycolmonomethylether, pyridine, or a mixture thereof.

In addition, since a base can facilitate the completion of the reaction 1 by scavenging the halogenated hydrogen produced during the reaction, it is preferable to add a base to the reaction mixture unless the used solvent is basic(for example, pyridine). Conventional inorganic or organic bases such as alkali metal hydroxide, alkali metal carbonate, organic amine and amidine can be used in this reaction. In particular, it is preferable to use one or more bases selected from a group consisting of sodium hydroxide, potassium hydroxide, triethylamine, pyridine, picoline, ruthidine, 1,4-diazabicyclo[2.2.2]-octane(DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU), 1,5-diazabicyclo[4.3.0]non-5-ene(DBN) or excessive amount of the amine compound of formula (III).

The above reaction 1 can be conducted preferably at the temperature of 15 to 200°C, more preferably at 60 to 120°C or reflux temperature of the solvent used.

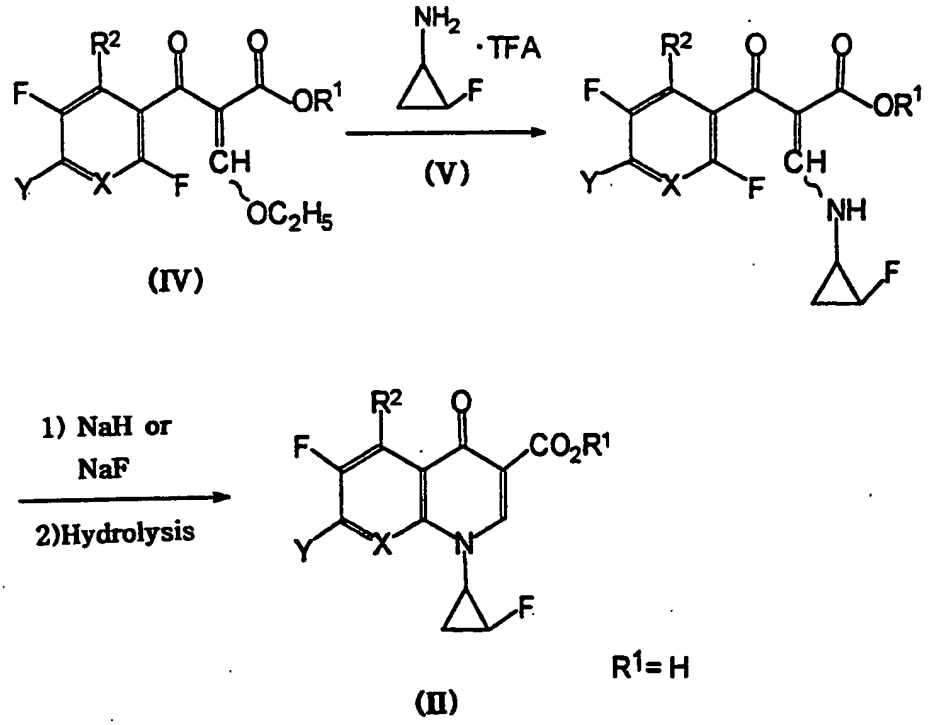
Although the reaction can be carried out for several days, it is advantageous to carry out for 1 to 24 hours, and conventionally, higher reaction temperature may have an effect of shortening the reaction time.

In this reaction, the amine compound of formula (III) can be used in the form of an inorganic or an organic acid

salt such as hydrochloride, hydrobromide, sulfate, formate, acetate and oxalate. And, the reactant (III) is preferably used in an amount of 1 to 6 times equivalence with respect to the quinoline carboxylic acid derivative (II).

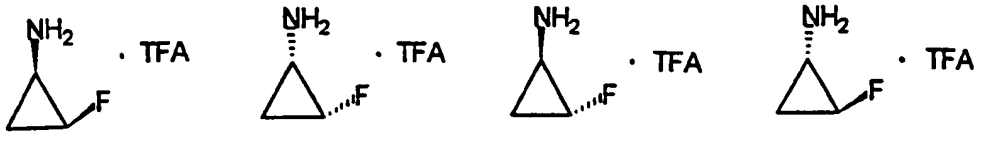
The compound of formula (II) used as the starting material in the above reaction scheme 1 is a known compound and can be readily prepared according to a method known in the prior publication, for example European Patent Application Nos. 191,185-A_1 and 341,493-A_2, as depicted in the following reaction scheme 2.

Reaction Scheme 2



The 2-fluorocyclopropylamine compound of formula (V)

used for preparing the compound of formula (II) in the above reaction scheme 2 can be existed as the following four stereochemical isomeric forms ;

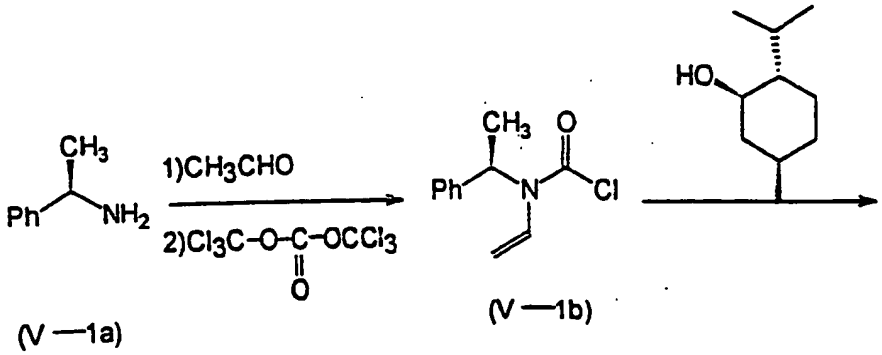


(V—1) , (V—2) , (V— 3) , (V—4)

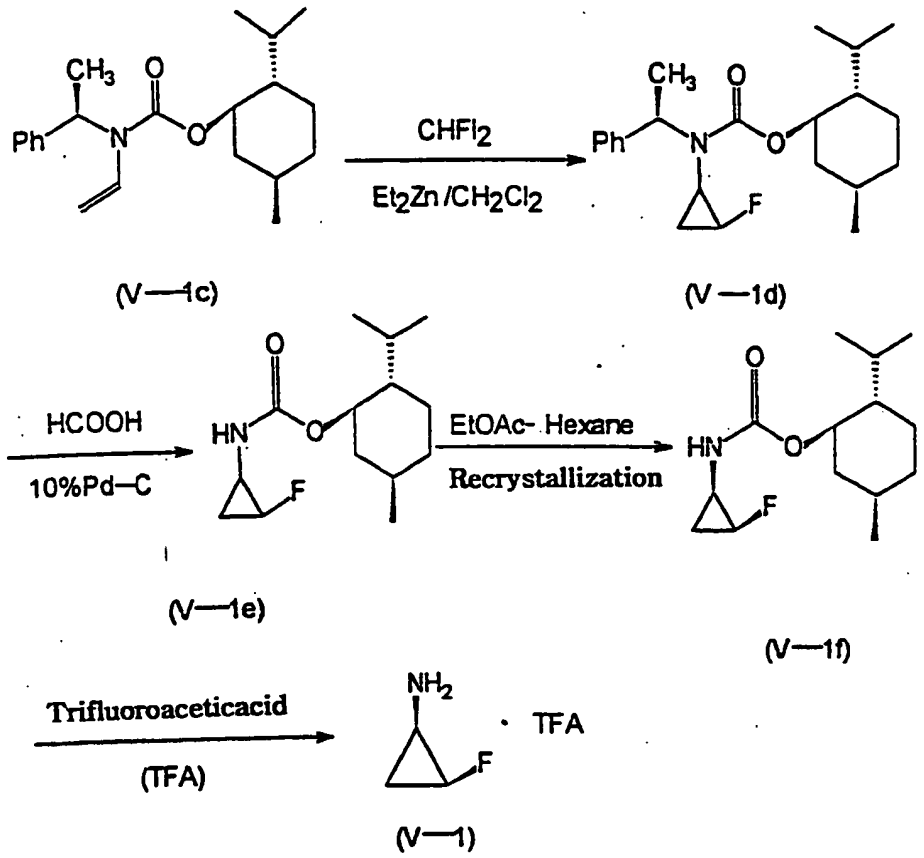
and each isomers in above may be used in the present invention as a pure isomer or a mixture thereof. However, it is most preferable to use the (1R,2S) isomer of the formula (V-1) among them.

In addition, said compound of formula (V-1) can be prepared according to a modified method of the known one(see: Tetrahedron Lett., 33(24), 3483-3486) as depicted in the following reaction scheme 3.

Reaction Scheme 3



(V—1a) (V—1b)

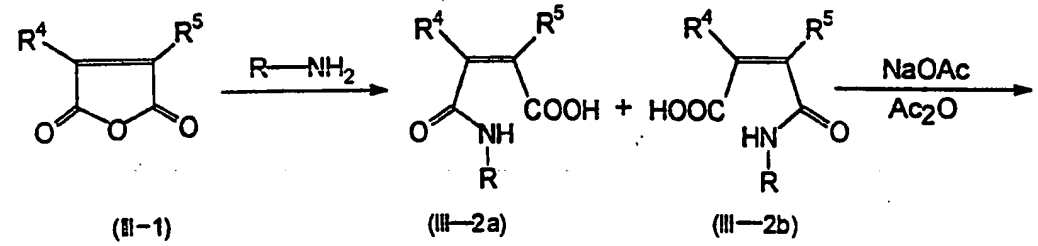


According to the reaction scheme 3 which represents the synthesis of the compound of formula (V-1), first a R-(+)-methylbenzylamine of the formula (V-1a) can be reacted with an acetaldehyde to obtain an imine compound, which is then reacted with bistrichloromethylcarbonate to prepare a N-vinylcarbamoylchloride of the formula (V-1b). Thus prepared compound (V-1b) is treated with l-(-)-menthol to obtain a carbamate compound of formula (V-1c) and the N-vinyl group in the compound (V-1c) is reacted with carbene to prepare a compound of formula (V-1d). Then, one side amino protecting group of the compound of formula (V-1d) is removed by means of Pd-C/HCOOH to synthesize a compound of formula (V-1e), which is then recrystallized 3 to 5

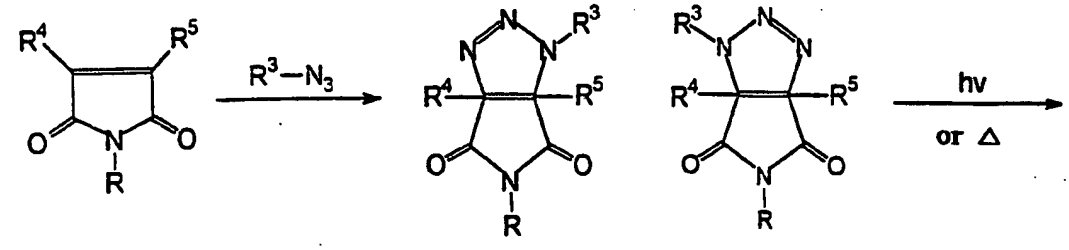
times in a mixture of ethylacetate/hexane solvents to obtain an optically active compound of formula (V-1f). Subsequently, the desired amine compound of formula (V-1) can be prepared with the isomeric purity over 97% by deprotecting the carbamate of formula (V-1f) using a trifluoroacetic acid.

While, the amine compound of formula (III) used as another reactant for preparing the compound of formula (I) has been disclosed in WO 92/12155 by the present inventors, and can be readily prepared according to the methods as depicted in the following reaction schemes 4, 5 or 6 respectively.

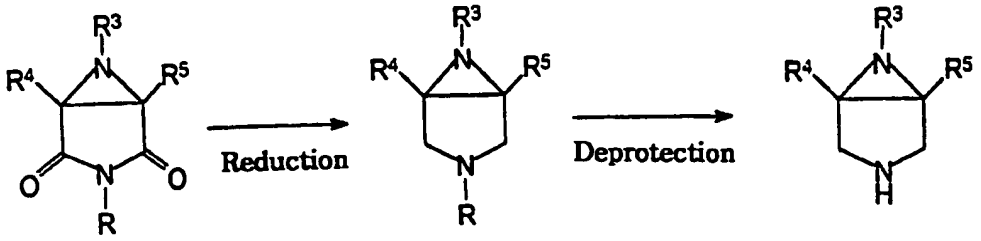
Reaction Scheme 4



(II-1) (III—2a) (III—2b)



(III—3) (III—4a) (III— 4b)



(III—5) (III—6) (III)

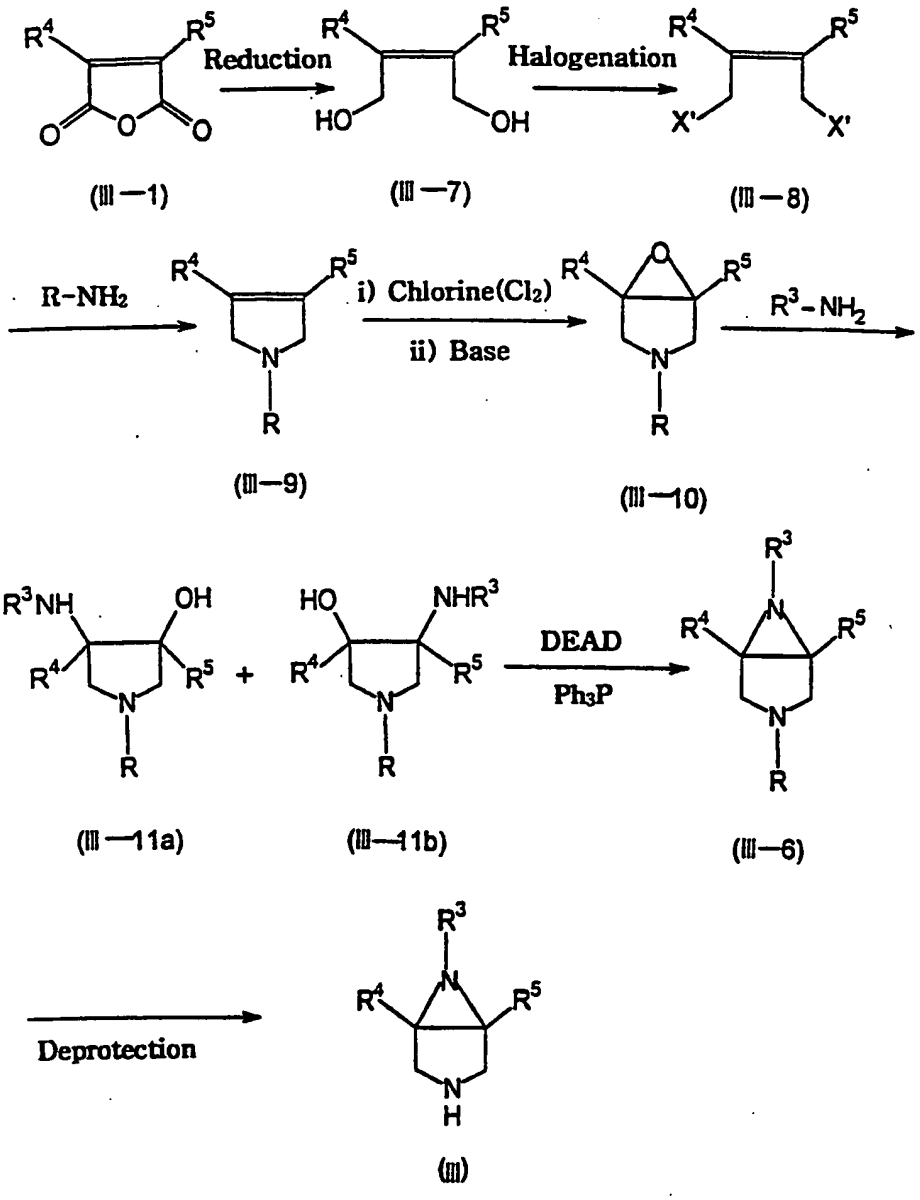
in the above reaction scheme 4,

R represents an amino protecting group which can be removed by acid or base hydrolysis, or hydrogenolysis; and

R^3, R^4 and R^5 are defined as previously described.

According to the reaction scheme 4, an maleic anhydride compound (III-1) as a starting material is reacted with benzylamine or substituted derivative thereof to obtain a maleaminic acid compound (III-2a + III-2b), which is then cyclized to a maleimide compound of formula (III-3) in the presence of acetic anhydride and sodium acetate. Then, the resulting maleimide compound (III-3) is treated with an azide compound (R^3-N_3) under 1,3-dipolar cycloaddition reaction to synthesize a triazoline compound (III-4a + III-4b), which is then subjected to photolytic or pyrolytic reaction to obtain a compound of formula (III-5) in a combined form of aziridine and pyrrolidine ring. The imide group among the compound (III-5) thus obtained is reduced with a reductant such as lithium aluminium hydride to prepare a compound (III-6), which is then deprotected by hydrolysis or hydrogenolysis to obtain the desired amine compound of formula (III).

Reaction Scheme 5



(III—1) (III—7) (III—8)

(III—9) (III—10)

(III—11a) (III—11b) (III—6)

(III)

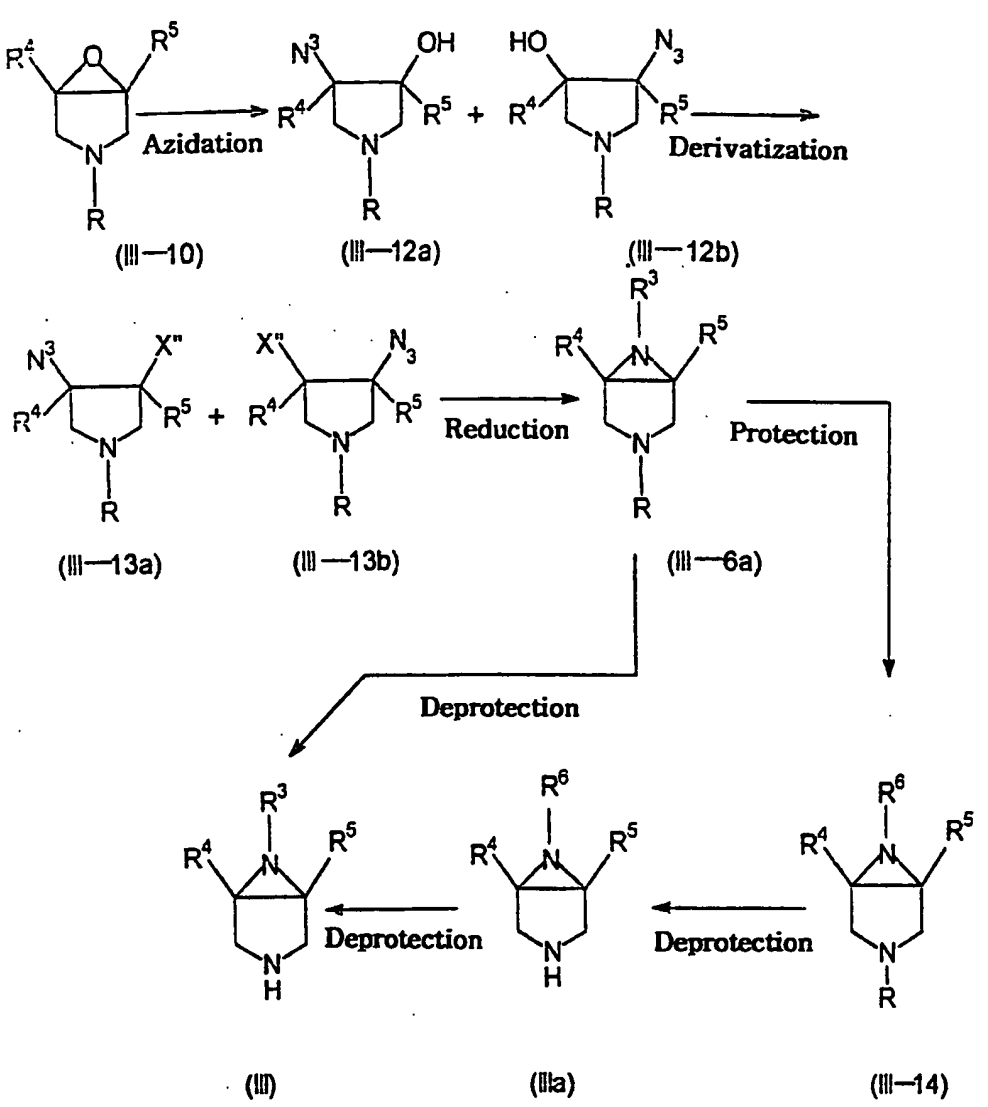
in the above reaction scheme 5,

X' represents a halogen such as chlorine or bromine; and

R, R^3, R^4 and R^5 are defined as previously described.

According to the method depicted in the reaction scheme 5, a compound of formula (III-8)(it can be commercially purchased when R^4 and R^5 respectively represent hydrogen, or it can be prepared by reducing first a maleic anhydride derivative of formula (III-1) to a compound of formula (III-7) and then halogenating the hydroxy groups of the compound (III-7) when R^4 and R^5 respectively represent an alkyl) is cyclized with an amine compound($R-NH_2$) to prepare a 3-pyrroline derivative of formula (III-9). Thus prepared 3-pyrroline derivative (III-9) is treated with chlorine gas to obtain a chlorohydrin derivative, which is then reacted with a base to synthesize an epoxide compound of formula (III-10). From the compound (III-10), a mixture of aminoalcohol compounds (III-11a) and (III-11b) can be prepared by means of an addition reaction using amine compound(R^3-NH_2) as a reactant. The resulting mixture is treated with diethylazodicarboxylate(DEAD) and triphenylphosphine(Ph_3P) to obtain the aziridine compound of formula (III-6), which is then deprotected to obtain the desired amine compound (III).

Reaction Scheme 6



in the above reaction scheme 6,

R^6 represents an amino protecting group which can be readily removed by acid or base hydrolysis or hydrogenolysis;

X" represents a leaving group such as halogen, methanesulfonyloxy, paratoluenesulfonyloxy, diethylphosphoryloxy, diethylthiophosphoryloxy, acetoxy or alkoxy; and R, R^3, R^4 and R^5 are defined as previously described.

According to the method of reaction scheme 6, a compound of formula (III-10) is reacted with sodium azide(NaN_3) to obtain an azidoalcohol mixture of compounds (III-12a) and (III-12b). And subsequently, these compounds can be converted to a mixture of compounds (III-13a) and (III-13b) due to a derivazation of the alcohol groups with a suitable leaving group. The mixture thus prepared is reduced to an azide compound of formula (III-6a) and finally the desired compound of formula (III) can be produced by deprotecting directly the compound (III-6a) or by introducing a protecting group to the aziridine ring and then removing the protecting group from the pyrrolidine ring and aqiridine ring succesively.

The synthetic methods as mentioned above will be more specifically explained in the following preparations and examples.

The present invention also provides an antibacterial composition comprising at least one quinoline compound of formula (I) defined above or a pharmaceutically acceptable salt thereof as an active component, together with a pharmaceutically acceptable carrier.

As established by the biological examples hereinbelow, the compound of formula (I) which is desired by the present invention shows a broad antibacterial spectrum and a potent antibacterial activity against gram-positive and gram-negative strains. Especially, the present compound (I) exhibits a highly excellent activity against resistant strains which cause serious problems recently.

The compound (I) according to the present invention also shows a similar or very high bioavailability in comparison to the prior agents in view of the pharmacokinetic property. And after the compound is absorbed into a living body, since it is distributed broadly and in high concentration over each organs it can be applied to both topical and generalized bacterial infections.

Moreover, since the compound according to the present invention is less toxic, it can be effectively used for antibiotic treatment of diseases caused by sensitive bacterial infections in warm-blooded animals including human being. And it can also be used as a washing solution for surface suppression of the growth of bacteria on a contact surface.

Sensitive strains, the growth of which is prevented by the compound (I) according to the present invention, generally include the gram-positive or gram-negative and aerobic or anaerobic strains such as Staphylococcus, Lactobacillus, Streptococcus, Sarcina, Escherichia, Enterobacter, Klebsiella, Pseudomonas, Acinetobacter, Proteus, Citrobacter, Nisseria, Baccullus, Bacteroides, Peptococcus, Clostridium, Salmonella, Shigella, Serratia, Haemophilus, Brucella, etc.

When the compound according to the present invention is used as an antibacterial agent, it may be formulated into pharmaceutical compositions for parenteral injection, oral administration in solid or liquid phase or rectal administration, or into a patchs by combining the compound of formula (I) with a pharmaceutically acceptable inert carrier.

Among them, the injectable preparation for parenteral administration may be prepared in the form of sterile aqueous or nonaqueous solution, suspension, or emulsion.

And a nonaqueous carrier, diluents, solvents or excipients which can be appropriately used include propyleneglycol, polyethyleneglycol, vegitable oils(for example, olive oil, sesame oil), organic ester for injection(for example, ethyloleate). These compositions can be sterilized by filtering or incorporating a sterilizing agent into a solid composition which can be solubilized in sterilized water or other sterilized injectable carrier.

The solid preparation for oral administration includes capsules, tablets, pills, powders and granules. In these solid preparations, the active ingredient is mixed with one or more inert solid carriers selected from the group consisting of sucrose, lactose, dicalciumphosphate, cellulose, pectin, dextrin, gelatine and starch. In addition, as in a conventional method, the solid preparation can comprise an additional component(for example, lubricants such as magnesium stearate) besides the inert solid carrier and it can also comprise a buffering agent in the case of capsules, tablets or pills.

The liquid preparation for oral administration includes pharmaceutically acceptable emulsions, solutions, suspensions and syrups which are formulated by comprising adjuvants such as humectant, emulsifying agents, suspending agents, sweeteners, aromatics or flavoring agents including inert diluents.

The composition for rectal administration includes suppository which can comprise excipients such as a cocoa oil or a wax for suppository besides the active ingredient.

On the other hand, the aforementioned patchs comprise a pharmaceutically acceptable carrier and a metal salt of the compound of formula (I). The carrier can be a hydrophilic carrier or an oil-water one which are dispersive in

water, especially a water-dispersive carrier or an aqueous oil-water emulsions in a form of semi-soft or cream type. Said carriers can be used with minimum indisposition on the burned or infected surface. This composition can also be prepared by mixing simply or homogeneously the micronized active component with a hydrophilic carrier or a basic plaster.

The amount of active compound in the composition according to the present invention can be varied depending on the pathway of administration to produce the desired antibacterial activity effectively. Therefore, the dosage level can be determined according to various factors such as efficacy of the active compound to be used, administration pathway, expected treatment period, etc.

In general, when the compound of formula (I) is administered orally to a mammal infected with a sensitive strain, the effective daily amount is about 0.5 to 500 mg of the active ingredient per kg of body weight. If required, the daily amount can be administered over several times, for example 2 to 4 times at appropriate intervals throughout a day. Those skilled in the art could easily determine the effective daily amount depending on the specific conditions.

The present invention will be more specifically explained in the following examples. However, it should be understood that the following preparations and examples are intended to illustrate the present invention and not to restrict the scope of the present invention in any manner.

Preparation 1
Synthesis of N-benzylmaleaminic acid

9.8g (0.10 mole) of maleic anhydride was dissolved in 150 ml of methylene chloride and to this solution was added dropwise 10.7g (0.10 mole) of benzylamine for 30 minutes at room temperature. After stirring for 3 hours at normal temperature, the mixture was filtered off, washed with methylene chloride, refiltered and dried to obtain 17.8g(Yield: 87%) of the title compound having white colour.

mp. 135-136°C
^{1}H NMR ($CDCl_3$): δ 4.2(s,2H), 6.0-7.9(m,7H), 9.7(s,1H), 13.0-16.0(broad s,1H)

Preparation 2
Synthesis of N-benzylmaleimide

5g(24 mmole) of N-benzylmaleaminic acid and 1.2g of sodium acetate were mixed in 12ml of acetic anhydride and the mixture was stirred for 1.5 hours at 95 to 105°C. After stirring, the reaction solution was poured into 50g of micronized ice and stirred for 2 hours by a mechanical stirrer. Water phase was removed from the solution and to the semi-solid dark brown product thus obtained was added 500 ml of ether. Then, after stirring for 20 minutes and removing the ether-insoluble dark brown solid by filtration, the ether filtrate was washed with aqueous sodium bicarbonate solution. The ether phase was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to remove the ether and then the residue was recrystallized from ethanol to obtain 2g (Yield: 44%) of the title compound having pale yellow colour.

mp. 67-68°C

^{1}H-NMR ($CDCl_3$): δ 4.6(s,2H), 6.6(s,2H), 7.3(s,5H),

Preparation 3

Synthesis of 2-methyl-2,3,4,7-tetraazabicyclo[3.3.0]oc-3-ten-6,8-dione

480ml of water was introduced into a 1 L 3-neck flask equipped with a thermometer, dropping funnel and condenser, and 8.46g (0.13 mole) of sodium azide and 21g of sodium hydrogen carbonate-sodium carbonate (1:1 mole ratio) were added thereto and then dissolved. The reaction solution was warmed under oil bath. On the other hand, 4g (21.4 mmole) of N-benzylmaleimide was dissolved in 100ml of toluene and then the resulting solution was cooled to -50 to -78°C under dry ice-acetone bath.

A conduit was connected in order to transfer the methane azide produced in the reaction vessel to the N-benzylmaleimide solution and a sodium hydroxide trap was installed in the middle of the conduit. While maintaining the temperature of the aqueous solution in the reaction vessel at 75 to 85°C, 37.2ml (0.4 mole) of dimethylsulfate was added dropwise over 40 minutes and then the flask containing N-benzylmaleimide solution was removed from the dryice-acetone bath. The flask was allowed to stand after the internal temperature being elevated to normal temperture.

The resulting white crystal was obtained by filtration and then it was combined with the residual crystal obtained after removing toluene from the filtrate. The combined crystal was washed with ether, filtered and dried to obtain 4.8g (Yield: 93%) of the title compound having white colour.

mp. 139°C

^{1}H-NMR ($CDCl_3$): δ 3.4(s,3H), 4.1(d,1H,J=12.0Hz),

4.6(s,2H), 5.4(d,1H,J=12.0Hz), 7.2(s,5H)

Preparation 4

Synthesis of 3-benzyl-6-methyl-3,6-diazabicyclo[3.1.0]hexan-2,4-dione

Method A : Photolysis reaction

300ml of 1,4-dioxane was introduced into a 500ml quartz reactor and then 4.0g (12.3 mmole) of 2-methyl-2,3,4,7-tetraazabicyclo[3.3.0]oc-3-ten-6,8-dione was added thereto and dissolved. After bubbling nitrogen gas through the reactor over 15 minutes, the reaction solution was irradiated with a 254nm ultraviolet lamp for 4 hours. The 1,4-dioxane was removed under reduced pressure and the residue was recrystallized from isopropylether to obtain 2.2g (Yield: 62%) of the title compound having pale yellow colour.

mp. 78-80°C

^{1}H-NMR ($CDCl_3$): δ 2.4(s,3H), 2.8(s,2H), 4.5(s,2H), 7.3(s,5H)

Method B : Pyrolysis reaction

13.7g (56.1 mmole) of 2-methyl-2,3,4,7-tetraazabicyclo[3.3.0]oc-3-ten-6,8-dione was dissolved in 300ml of xylene(o-, m- and p- mixture) and the reaction solution was refluxed and stirred for 7 hours. After the xylene was removed under reduced pressure, the residue was partially purified with column chromatography (eluent; ethyl acetate:hexane = 1:3) and recrystallized from isopropylether over 3 or 4 times to obtain 3.6g (Yield : 30%) of the title compound having pale yellow colour.

mp and ^{1}H-NMR data are identical to those of Method A.

Preparation 5

Synthesis of 3-benzyl-6-methyl-3,6-diazabicyclo[3.1.0]hexane

1.76g (46.3 mmole) of lithium aluminum hydride was added dropwise to 50ml of dry tetrahydrofuran at normal temperature and to the mixture was added dropwise 5g (23.1 mmole) of 3-benzyl-6-methyl-3,6-diazabicyclo[3.1.0]hexan-2,4-dione which was dissolved in 15ml of dry tetrahydrofuran.

After the addition is completed, the reaction solution was stirred for 3 hours under refluxing and cooled under ice bath. Then, 0.85ml of water, 0.85ml of 15%-KOH and 2.5ml of water were succesively added thereto while maintaining the temperature around 10°C. The tetrahydrofuran was removed under reduced pressure and to the residue was added 100ml of chloroform to extract a product. Then, the product was washed with water and saturated sodium chloride solution, dried and filtered.

Under reduced pressure, the chloroform was removed to obtain 4g of crude product having brown colour, which was then purified by column chromatography (eluent; ethanol : ethyl acetate = 1:4) to obtain 1.44g (Yield: 33%) of the title compound as a yellow oil.

^{1}H-NMR ($CDCl_3$): δ 2.0(s,2H), 2.2(s,3H), 2.3(dd,2H), 3.1(d,2H,J=12.0Hz), 3.6(s,2H), 7.3(s,5H)

Preparation 6

Synthesis of 6-methyl-3,6-diazabicyclo[3.1.0]hexane acetate

1.0g (5.3 mmole) of 3-benzyl-6-methyl-3,6-diazabicyclo[3.1.0]hexane was dissolved in 100ml of methanol. Then, 0.32g (304μl, 5.3 milimole) of acetic acid and 1.0g

of 10% Pd-C catalyst were added thereto and the mixture was reacted for one hour at normal temperature under 60psi of hydrogen pressure.

After reacting, the reaction solution was filtered through cellite and the methanol was removed from the filtrate under reduced pressure to obtain 0.78g (Yield: 93%) of the title compound as a light brown semi-solid.

^{1}H-NMR ($CDCl_3$): δ 2.0(s,3H), 2.1(s,2H), 2.3(s,3H), 2.8(d,2H,J=12.0Hz),3.2(d,2H,J=12.0Hz), 7.4(s,1H), 8.2(broad s,2H)

Preparation 7

Synthesis of 1-benzyl-3-pyrroline

12.5g (0.10 mole) of cis-1,4-dichloro-2-butene was dissolved in 400ml of benzene and then 33.2g (0.31 mole) of benzylamine was added dropwise thereto at normal temperature. After stirring for one hour, the reaction mixture was allowed to stand overnight. The thus obtained solid was removed by filtration and then the filtrate was washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified with column chromatography (eluent; ethyl acetate:n-hexane = 1:3) to obtain 13.5g (Yield: 85%) of the title compound as a pale yellow oil.

^{1}H-NMR ($CDCl_3$): δ 3.4(s,4H), 3.7(s,2H), 5.8(s,2H), 7.2(s,5H)

Preparation 8

Synthesis of 1-benzyl-3,4-epoxypyrrolidine

100ml of distilled water and 10ml of concentrated hydrochloric acid were added to 16g (0.1 mole) of 1-benzyl-3-pyrroline and through this solution chlorine gas was

passed for 30 minutes. The resulting solution was adjusted to pH 9 to 10 by adding aqueous 20%-NaOH solution dropwise and then extracted with 500ml of methylene chloride. The extract was concentrated under reduced pressure and 100ml of aqueous 20%-NaOH solution was added thereto. After stirring overnight at normal temperature, the solution was extracted with 500 ml of methylene chloride again, dried and concentrated under reduced pressure. The residue was purified with column chromatography to obtain 11.5g (Yield: 66%) of the title compound as a light brown oil.

^{1}H-NMR ($CDCl_3$): δ 2.5(d,2H,J=12Hz), 3.2(d,2H,J=12Hz), 3.5(s,2H), 3.7(s,2H), 7.3(s,5H)

Preparation 9

Synthesis of 1-benzyl-trans-4-azido-3-hydroxypyrrolidine

6g (34 mmole) of 1-benzyl-3,4-epoxypyrrolidine was dissolved in 200ml of acetone-water (1:1 by volume) and 13.4g (0.21 mole) of sodium azide was added thereto. The reaction mixture was refluxed overnight, and then concentrated under reduced pressure, extracted with 200ml of chloroform(2x) and dried over anhydrous magnesium sulfate.

After filtration, the filtrate was concentrated under reduced pressure and the residue was purified with column chromatography (eluent; ethyl acetate:n-hexane = 1:1) to obtain 6.8g (Yield: 92%) of the title compound as a reddish brown oil.

^{1}H-NMR ($CDCl_3$): δ 2.1-3.3(m,5H), 3.6(s,2H), 3.5-3.9(m,1H), 4.1-4.3(m,1H), 7.3(s,5H)

Preparation 10
Synthesis of 1-benzyl-trans-4-azido-3-mesyloxypyrrolidine

5.0g (23 mmole) of 1-benzyl-trans-4-azido-3-hydroxy-pyrrolidine was dissolved in 150ml of dry benzene and the whole was cooled down under ice bath. Then, 3.0g (30 mmole) of triethylamine was added to the mixture and 3.2g (28 mmole) of methanesulfonylchloride dissolved in 20ml of dry benzene was added dropwise over 10 minutes thereto. After stirring for 2 hours at normal temperature, 1ml of water was slowly added thereto and the mixture was introduced into a separating funnel and then washed with water. A benzene layer separated from the mixture was dried, concentrated under reduced pressure and purified with column chromatography (eluent; ethyl acetate:n-hexane = 1:3) to obtain 6.4g (Yield: 95%) of the title compound as a reddish brown oil.

^{1}H-NMR ($CDCl_3$): δ 2.4-3.2(m,4H), 3.0(s,3H), 3.6(s,2H), 3.9-4.2(m,1H), 4.8-5.1(m,1H), 7.3(s,5H)

Preparation 11
Synthesis of 3-benzyl-3,6-diazabicyclo[3.1.0]hexane

1.0g (3.4 mmole) of 1-benzyl-trans-4-azido-3-mesyl-oxypyrrolidine was dissolved in 30ml of dry ether and then 0.25g (6.8 mmole) of lithium aluminum hydride was added dropwise thereto. After stirring for 2 hours at normal temperature, 0.15ml of water, 0.5ml of 15%-KOH and 0.5ml of water were added succesively to the mixture and then 20ml of ether-acetone (1:1 by volume) was added thereto. Then, the whole mixture was filtered, dried and concentrated under reduced pressure and the residue was subjected to column chromatography (eluent; ethanol:ethyl acetate = 1:3) to obtain 0.50g (Yield: 85%) of the title compound as a yellow oil.

^{1}H-NMR ($CDCl_3$): δ 1.8(broad s,1H), 2.3(d,2H,J=10Hz), 2.4(s,2H), 3.1(d,2H,J=10Hz), 3.6(s,2H), 7.2(s,5H)

Preparation 12

Synthesis of 3,6-diazabicyclo[3.1.0]hexane

0.5g (2.9 mmole) of 3-benzyl-3,6-diazabicyclo[3.1.0]-hexane was dissolved in 60ml of methanol, and 170μl (2.9 mmole) of acetic acid and 0.5g of 10% Pd-C catalyst were added thereto. Then, the whole mixture was reacted for one hour at 50psi of hydrogen pressure in Parr reactor. The reaction solution was filtered through cellite and the methanol contained in the filtrate was removed under reduced pressure to obtain 0.39g of the acetate of the title compound as a crude state. This crude product was purified with column chromatography (eluent; methanol:40%-methyl amine = 24:1) to obtain 0.12g (Yield: 45%) of the title compound as a colorless transparent oil.

^{1}H-NMR ($CDCl_3$): δ 1.4(s,2H), 2.5(s,2H), 2.9(q,4H, J=12Hz)

Preparation 13

Synthesis of 3-benzyl-6-methoxycarbonyl-3,6-diazabicyclo [3.1.0]hexane

3.5g (20 mmole) of 3-benzyl-3,6-diazabicyclo[3.1.0] hexane was dissolved in 100ml of dry benzene, and then to the mixture was added 2.4g (24 mmole) of triethylamine and was added dropwise 2.1g (22 mmole) of methyl chloroformate dissolved in 20ml of dry benzene over 15 minutes. The resulting solution was stirred for 2 and a half hours at normal temperature and filtered. The filtrate was washed with water and then dried over anhydrous magnesium sulfate. After drying, the solution was filtered again and the filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography (elu-

ent; ethyl acetate:n-hexane = 1:3) to obtain 4.3g (Yield: 92%) of the title compound as a reddish brown oil.

^{1}H-NMR ($CDCl_3$): δ 2.3(d,2H,J=10Hz), 2.9(s,2H), 3.3(d,2H,J=10Hz), 3.6(s,2H), 3.7(s,3H), 7.3(s,5H)

Preparation 14

Synthesis of 6-methoxycarbonyl-3,6-diazabicyclo[3.1.0]hexane

1.5g (6.5 mmole) of 3-benzyl-6-methoxycarbonyl-3,6-diazabicyclo[3.1.0]hexane was dissolved in 100ml of methanol and 0.75g of 10% Pd-C catalyst was added thereto. Then, the mixture was reacted for 4 and a half hours under 50psi of hydrogen pressure. The resulting reaction solution was filtered through cellite and the filtrate was concentrated under reduced pressure. The residue was separated and purified with column chromatography (eluent; ethanol:ethyl acetate = 1:3) to obtain 0.60g (Yield : 65%) of the title compound as a white solid.

mp. 80°C

^{1}H-NMR ($CDCl_3$): δ 1.3(broad s,1H), 2.7(s,2H), 3.3(d,2H,J=12Hz), 3.6(s,3H), 3.6(d,2H,J=12Hz)

Preparation 15

Synthesis of 3,6-diazabicyclo[3.1.0]hexane acetate

1.5g (11 mmole) of 6-methoxycarbonyl-3,6-diazabicyclo[3.1.0]hexane was dissolved in 35ml of methanol and 3g of NaOH was added thereto. This solution was stirred overnight at 70 to 80°C and then 4.5g of acetic acid was added dropwise under ice bath. The resulting reaction solution was concentrated under reduced pressure, dried in high vacuum and then extracted with 100ml of chloroform. The chloroform from the extract was removed under reduced

pressure to obtain 1.34g (Yield: 88%) of the title compound as a semi-solid.

^{1}H-NMR ($CDCl_3$): δ 1.9(s,3H), 2.7(s,2H), 3.0(q,4H, 12Hz), 3.4(s,2H), 5.6(broad s,1H)

Preparation 16

Synthesis of cis-1,4-dihydroxy-2-methyl-2-butene

6.7g (0.18 mole) of lithium aluminum hydride was slowly added to 300ml of dry tetrahydrofuran and then 10.0g (0.089 mole) of dry citraconic acid dissolved in 30ml of dry tetrahydrofuran was added dropwise to that solution at -20 to -10°C. The resulting solution was stirred for one hour at the same temperature and adjusted to pH 7 to 8 by adding dropwise 30% aqueous sulfuric acid solution thereto and then filtered. The filter cake was washed with 300ml of ether-acetone (1:1 by volume) and filtered again. The two filtrates were combined together and dried over anhydrous sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified with column chromatography (eluent; ethyl acetate) to obtain 1.1g (Yield: 12%) of the title compound as a yellow oil.

^{1}H-NMR ($CDCl_3$): δ 1.7(s,3H), 3.2-3.8(m,2H), 3.9-4.2(m,4H), 5.5(t,1H,J=8Hz)

Preparation 17

Synthesis of cis-1,4-dibromo-2-methyl-2-butene

1.0g (9.8 mmole) of cis-1,4-dihydroxy-2-methyl-2-butene was dissolved in 30ml of dry methylene chloride and then 2.3g (23 mmole) of triethylamine was added thereto. To the mixture was added dropwise 5.9g (22 mmole) of phosphorus tribromide while the whole mixture was cooled down under ice bath. After stirring for 1.5 hours, 1ml

of water was added to the reaction solution, which was then introduced into a separating funnel. Then, this reaction solution was washed with 10ml of water and the methylene chloride phase was separated and dried. After filtration, the filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography (eluent; ethyl acetate:n-hexane = 1:4) to obtain 1.5g (Yield: 67%) of the title compound as a light yellow oil.

^{1}H-NMR ($CDCl_3$): δ 1.9(s,3H), 4.0-4.2(m,4H), 5.6(t,1H)

Preparation 18
Synthesis of 1-benzyl-3-methyl-3-pyrroline

3.0g (13 mmole) of cis-1,4-dibromo-2-methyl-2-butene was dissolved in 120ml of benzene and then 4.4g (41 mmole) of benzylamine was added dropwise at normal temperature. Then, the reaction solution was stirred for 30 minutes and was allowed to stand overnight. After standing, the produced solid was removed by filtration and the filtrate was washed with water and dried. After drying, the solution was filtered again and the filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography (eluent; ethyl acetate:n-hexane = 1:3) to obtain 1.6g (Yield: 70%) of the title compound as a yellow oil.

^{1}H-NMR ($CDCl_3$): δ 1.7(s,3H), 3.4(s,4H), 3.7(s,2H), 5.4(s,1H), 7.3(s,5H)

Preparation 19
Synthesis of 1-benzyl-3,4-epoxy-3-methylpyrrolidine

10ml of H_2O and 1ml of concentrated hydrochloric acid were added to 1.0g (5.7 mmole) of 1-benzyl-3-methyl-3-pyrroline and then chlorine gas was passed for 20 minutes

through this solution. The resulting solution was adjusted to pH 9 to 10 by adding 20%-NaOH dropwise and then extracted with 50ml of methylene chloride. The extract was concentrated under reduced pressure and to the residue was added 5ml of 20%-NaOH.

After stirring overnight at normal temperature, the resulting solution was extracted with 50ml of methylene chloride(2x), dried, concentrated under reduced pressure and subjected to column chromatography (eluent; ethyl acetate:n-hexane = 2:1) to obtain 0.68g (Yield: 62%) of the title compound as a yellowish brown oil.

^{1}H-NMR ($CDCl_3$): δ 1.5(s,3H), 2.2-2.7(m,2H), 2.9-3.3(m,2H), 3.4(s,1H), 3.7(s,2H), 7.3(s,5H)

Preparation 20

Synthesis of a mixture of 1-benzyl-trans-4-azido-3-hydroxy-3-methylpyrrolidine and 1-benzyl-trans-4-azido-3-hydroxy-4-methylpyrrolidine

1.0g (5.3 mmole) of 1-benzyl-3,4-epoxy-3-methylpyrrolidine was dissolved in 30ml of dimethylformamide and 1.0g (15 mmole) of sodium azide and 0.03g (0.56 mmole) of ammonium chloride were added thereto, and then the resulting solution was stirred overnight at 75 to 80°C. 30ml of chloroform was added to the solution , which was then filtered and concentrated under reduced pressure. To the residue was added 50ml of chloroform and the mixture was filtered again.

The filtrate was concentrated under reduced pressure and the residue was purified with column chromatography (eluent; ethyl acetate:n-hexane = 1:1) to obtain 0.92g (Yield: 75%) of the title compound as a reddish brown oil.

^{1}H-NMR ($CDCl_3$): δ 1.3(s,3H), 2.1-3.4(m,5H), 3.6(s,2H),

3.8-4.1(m,1H), 7.3(s,5H)

Preparation 21

Synthesis of a mixture of 1-benzyl-trans-4-azido-3-mesyloxy-3-methylpyrrolidine and 1-benzyl-trans-4-azido-3-mesyloxy-4-methylpyrrolidine

2.0g (8.6 mmole) of the azido alcohol (the compound prepared in Preparation 20 above) was dissolved in 60ml of dry benzene and then the solution was cooled down under ice bath. To this solution was added 1.1g (11 mmole) of triethylamine and was added dropwise 1.2g (10 mmole) of methanesulfonylchloride over 5 minutes. After stirring for 8 hours at normal temperature, 0.5ml of water was slowly added and the resulting solution was introduced into a separating funnel and washed with water. The separated benzene layer was dried and concentrated under reduced pressure and then the residue was subjected to column chromatography (eluent; ethyl acetate:n-hexane = 1:5) to obtain 1.7g (Yield: 65%) of the title compound as a reddish brown oil.

^{1}H-NMR ($CDCl_3$): δ 1.4(s,3H), 2.5-3.5(m,4H), 3.0(s,3H), 3.6(s,2H), 4.6-4.9(m,1H), 7.3(s,5H)

Preparation 22

Synthesis of 3-benzyl-1-methyl-3,6-diazabicyclo[3.1.0]hexane

1.0g (3.2 mmole) of azidomesylate(the compound prepared in Preparation 21 above) was dissolved in 30ml of dry ether and then 0.24g (6.5 mmole) of lithium aluminum hydride was added dropwise thereto. After stirring for 4 hours at normal temperature, 0.15ml of water, 0.5ml of 15% KOH and 0.5ml of water were succesively added to the solution and 30ml of ether-acetone (1:1 by volume) was added thereto. The resulting solution was filtered,

dried and concentrated under reduced pressure. The residue was purified with column chromatography (eluent; ethanol:ethyl acetate = 1:3) to obtain 0.46g (Yield: 76%) of the title compound as a yellow oil.

^{1}H-NMR ($CDCl_3$): δ 1.2(s,3H), 1.8(broad s,1H), 2.2(t,2H,J=10Hz), 2.9(t,2H,J=10Hz), 3.6(s,2H), 7.3(s,5H)

Preparation 23

Synthesis of 1-methyl-3,6-diazabicyclo[3.1.0]hexane acetate

0.5g (2.7 mmole) of 3-benzyl-1-methyl-3,6-diazabicyclo[3.1.0]hexane was dissolved in 60ml of methanol and to this solution were added 157μl (2.7 mmole) of acetic acid and 0.5g of 10% Pd-C catalyst. Then, the whole mixture was reacted for 1.5 hours under 50psi of hydrogen pressure in a Parr reactor. The reaction solution was filtered through cellite and the methanol was removed from the filtrate under reduced pressure to obtain 0.38g (Yield: 91%) of the title compound as an oil.

^{1}H NMR (D_2O): δ 1.3(s,3H), 1.8(s,3H), 2.7(s,1H), 3.2-3.4(m,4H)

Preparation 24

Synthesis of 1-benzyl-trans-3-hydroxy-4-methylaminopyrrolidine

5ml of 1,4-dioxane and 25ml of 40% aqueous methylamine solution were added to 1.0g (5.7 mmole) of 1-benzyl-3,4-epoxypyrrolidine and the whole was stirred overnight at 40 to 45°C. This solution was concentrated under reduced pressure and to the residue was added 30ml of chloroform. The resulting solution was dried over anhydrous magnesium sulfate and filtered. The chloroform was removed from

the filtrate under reduced pressure to obtain 1.1g (Yield: 94%) of the title compound as a yellowish brown oil.

^{1}H NMR ($CDCl_3$): δ 2.2-3.2(m,7H), 2.3(s,3H), 3.6(s,2H), 3.8-4.1(m,1H), 7.3(s,5H)

Preparation 25

Synthesis of 3-benzyl-6-methyl-3,6-diazabicyclo[3.1.0]hexane

2.0g (9.7 mmole) of 1-benzyl-trans-3-hydroxy-4-methylaminopyrrolidine was dissolved in 25ml of dry tetrahydrofuran and 3.1g (12 mmole) of triphenylphosphine was added thereto. This mixture was stirred under ice bath. 1.85ml (12 mmole) of diethylazodicarboxylate (DEAD) was added dropwise thereto and the resulting solution was stirred for one hour under ice bath and stirred for further 7 hours at normal temperature. The solution was concentrated under reduced pressure and to the residue was added 30ml of ethyl acetate-petroleum ether (1:1 by volume) and then the produced crystal was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography (eluent; ethanol:acetate = 1:3) to obtain 1.25g (Yield: 69%) of the title compound as a reddish brown oil.

^{1}H NMR ($CDCl_3$): δ 2.0(s,2H), 2.2(s,3H), 2.3(dd,2H), 3.1(d,2H,J=12Hz), 3.6(s,2H), 7.3(s,5H)

Preparation 26

Synthesis of a mixture of 1-benzyl-trans-4-methylamino-3-hydroxy-3-methylpyrrolidine and 1-benzyl-trans-4-methylamino-3-hydroxy-4-methylpyrrolidine

1.0g (5.3 mmole) of 1-benzyl-3,4-epoxy-3-methylpyrrolidine was dissolved in 5ml of 1,4-dioxane and 30ml of 40% aqueous methylamine solution was added thereto. The

resulting solution was stirred overnight at 50 to 60°C and then concentrated under reduced pressure. After 30ml of chloroform was added to the residue, this solution was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to obtain 1.1g (Yield: 92%) of the title compound as a yellowish brown oil.

^{1}H NMR ($CDCl_3$): δ 1.3(s,3H), 2.0-3.8(m,7H), 2.4(s,3H), 3.6(s,2H), 7.3(s,5H)

Preparation 27

Synthesis of 3-benzyl-1,6-dimethyl-3,6-diazabicyclo[3.1.0] hexane

1.0g (4.5 mmole) of the aminoalcohol (the compound prepared in Preparation 26 above) was dissolved in 15ml of dry tetrahydrofuran and 1.4g (5.5 mmole) of triphenylphosphine was added thereto. To the whole mixture was added dropwise 0.9ml (5.7 mmole) of diethylazodicarboxylate while the mixture was stirred under ice bath. After stirring for one hour under ice bath, the mixture was stirred overnight further at normal temperature. The resulting solution was concentrated under reduced pressure and 20ml of ethyl acetate-petroleum ether (1:1 by volume) was added thereto. Then, the produced crystal was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography (eluent; ethanol:ethyl acetate = 1:3) to obtain 0.61g (Yield: 66%) of the title compound as a reddish brown oil.

^{1}H NMR ($CDCl_3$): δ 1.3(s,3H), 1.7(s,1H), 2.1-2.6(m,2H), 2.3(s,3H), 2.8-3.2(m,2H), 3.6(s,2H), 7.3(s,5H)

Preparation 28

Synthesis of N-(1-phenylethyl)-N-vinylcarbamoyl chloride

94.3g of R-(+)-α-methylbenzylamine was diluted with 900ml of ethylether and 450g of anhydrous magnesium sulfate was added thereto. The mixture was cooled down under ice water and then stirred vigorously while 80ml of acetaldehyde was added slowly thereto. The resulting solution was reacted for 3 hours and then the produced solid was filtered off, and the solvent contained in the filtrate was removed by distillation under reduced pressure. The residue was diluted with 900ml of toluene and 103ml of triethylamine was added thereto. The above solution was cooled down under ice water and to the solution was added slowly 84g of bistrichloromethylcarbonate (triphosgene) dissolved in 200ml of methylene chloride. After heating the reaction mixture for 3 hours at 80°C, it was cooled down to room temperature, washed twice with the same volume of water and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure and then the residue was distilled in high vacuum(about 3mmHg) to obtain 126g (Yield: 78%) of the colorless title compound which was distilled at 108 to 110°C.

^{1}H NMR ($CDCl_3$): δ 1.65(d,3H), 4.75(dd,1H), 5.63(q,1H), 6.56(dd,2H), 7.38(s,5H)

Preparation 29

Synthesis of L-(-)-menthyl N-(1-phenylethyl)-N-vinylcarbamate

81.4g of L-(-)-menthol and 12.5g of sodium hydride were succesively added to 600ml of N,N-dimethylformamide and dissolved thoroughly. This solution was cooled down in ice water and 91.0g of N-(1-phenylethyl)-N-vinylcarbamoylchloride dissolved in 100ml of N,N-

dimethylformamide was added slowly thereto. After stirring for 30 minutes at normal temperature, the reaction solution was poured into 1400ml of distilled water and extracted with 300ml of ethyl acetate twice. The combined extract was dried over anhydrous magnesium sulfate and the solvent was removed by distillation under reduced pressure. Then, the residue was purified with column chromatography (eluent; ethyl acetate:hexane = 1:10 by volume) to obtain 143g (Yield: 83%) of the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 0.7-2.0(m,21H), 4.30(dd,1H), 5.44(m,1H), 6.96(dd,2H), 7.30(s,5H)

Preparation 30

Synthesis of L-(-)menthyl N-(cis-2-fluoro-1-cyclopropyl)-N-(1-phenylethyl)carbamate

255ml (1.1M) of diethylzinc ($ZnEt_2$) dissolved in toluene was added slowly to a solution which 64.3g of L-(-)-menthyl N-(1-phenylethyl)-N-vinylcarbamate and 80.2g of fluorodiiodomethane ($CHFI_2$) were dissolved together in 500ml of dry methylene chloride while the whole mixture was cooled down in dryice-acetone under nitrogen atmosphere. After stirring for 30 minutes at the same temperature, the solution was allowed to stand so that it's temperature can be raised slowly. Then, the reaction solution was stirred for further 2 hours at normal temperature and 250ml of 1N-hydrochloric acid was added thereto. After stirring, the organic layer was separated and dried over anhydrous magnesium sulfate. After removing the solvent by distillation under reduced pressure, the residue was purified with column chromatography (eluent; ethyl acetate:hexane = 1:10 by volume) to obtain 49.4g (Yield: 70%) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$): δ 0.6-2.1(m,23H), 2.40(m,1H),

4.06(m,0.5H), 4.56(m,1H), 4.85(m,1H),
5.30(m,0.5H), 7.30(s,5H)

Preparation 31

Synthesis of L-(-)-menthyl N-(cis-2-fluoro-1-cyclopropyl)carbamate

9.0g of L-(-)-menthyl N-(cis-2-fluoro-1-cyclopropyl) N-(1-phenylethyl)carbamate was dissolved in a solution of 10%-formic acid/methanol(v/v) and 9.0g of 10%-Pd/C was added thereto. The reaction solution was stirred for one day at normal temperature and filtered through cellite. After the filtrate was distilled under reduced pressure, the residue was subjected to column chromatography (eluent; ethyl acetate:hexane = 1:8 by volume) to obtain 3.2g of the title compound as a white solid. The recovered starting material can be reacted again to obtain total 3.8g (Yield: 60%) of the title compound.

^{1}H NMR ($CDCl_3$): δ 0.7-2.1(m,20H), 2.63(m,1H),
4.15(m,0.5H), 4.55(m,1H), 4.91(m,0.5H)

Preparation 32

Synthesis of L-(-)-menthyl N-[(1R,2S)-2-fluoro-1-cyclopropyl]carbamate

10g of L-(-)-menthyl N-(cis-2-fluoro-1-cyclopropyl)-carbamate prepared in Preparation 31 was recrystallized four times from a mixture of ethyl acetate-hexane (1:10 by volume) to obtain 2.5g (Yield: 25%) of the title compound as a white crystal.

mp. 117-118°C (decomposed)
$[\alpha]_D^{20}$ = -44° (C 1.00, methanol)
^{1}H NMR ($CDCl_3$): δ 0.7-2.1(m,20H), 2.63(m,1H),
4.15(m,0.5H), 4.55(m,1H), 4.91(m,0.5H)

Preparation 33

Synthesis of (cis-2-fluoro-1-cyclopropyl)ammoniumtrifluoroacetate

1.0g of L-(-)-menthyl N-(cis-2-fluoro-1-cyclopropyl)-carbamate prepared in Preparation 31 was dissolved in 5ml of trifluoroacetic acid and the mixture was refluxed for 6 hours while heated. After cooling down to room temperature, the solvent was removed by distillation under reduced pressure. After the residue was dispersed in 5ml of water and 5ml of methylene chloride, the water phase was separated and then the water was removed by distillation under reduced pressure. The produced oily material was allowed to stand at room temperature in order to obtain 0.8g (Yield: 100%) of the title compound as a pale yellow solid.

^1H NMR (D_2O): δ 1.20(m,1H), 1.41(m,1H), 2.71(m,1H), 4.49(m,0.5H), 5.14(m,0.5H)

Preparation 34

Synthesis of [(1R,2S)-2-fluoro-1-cyclopropyl]ammonium trifluoroacetate

0.8g (Yield: 100%) of the title compound was prepared according to the same procedure as Preparation 33 except that 1.0g of L-(-)-menthyl N-[(1R,2S)-2-fluoro-1-cyclopropyl)carbamate is used instead of 1.0g of L-(-)-menthyl N-(cis-2-fluoro-1-cyclopropyl)carbamate.

$[\alpha]_D^{20}$ = -14° (C 1.00, MeOH)

^1H NMR (D_2O): δ 1.20(m,1H), 1.41(m,1H), 2.71(m,1H), 4.49(m,0.5H), 5.14(m,0.5H)

Preparation 35

Synthesis of 8-chloro-6,7-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

Step (1): Synthesis of ethyl 3-(3-chloro-2,4,5-trifluorophenyl)-2-[(1R,2S)-2-fluoro-1-cyclopropyl)amino]methylene-3-oxopropionate;

4.48g of ethyl 3-(3-chloro-2,4,5-trifluorophenyl)-3-oxopropionate was dissolved in 15.1ml of acetic anhydride and 6.02ml of triethylorthoformate was added thereto. The reaction solution was refluxed for 3.5 hours and then the volatile component was removed by distillation under reduced pressure. The residue was diluted with 15ml of absolute ethanol and 4.22ml of triethylamine was added thereto. To this solution was added dropwise 3.0g of [(1R,2S)-2-fluoro-1-cyclopropyl]ammonium trifluoroacetate dissolved in 5ml of ethanol at 0°C. The resulting solution was stirred for 30 minutes at normal temperature and then the solvent was removed by distillation under reduced pressure. 50ml of chloroform was added to the residue and the mixture was washed with the same volume of water twice. The chloroform phase was dried over anhydrous magnesium sulfate and the solvent was removed by distillation under reduced pressure to obtain 4.9g (Yield: 86%) of the desired compound as a pale yellow solid.

mp. 93-95°C

$[\alpha]_D^{20}$ = +7.1° (C 1.00, $CHCl_3$)

^1H NMR ($CDCl_3$): δ 1.05(t,3H), 0.9-1.9(m,2H), 2.95(m,1H), 4.05(q,2H), 4.30(m,0.5H), 5.10(m,0.5H), 7.15(m,1H), 8.14, 8.31(2s,1H)

Step (2): Synthesis of ethyl 8-chloro-6,7-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylate;

4.9g of ethyl 3-(3-chloro-2,4,5-trifluorophenyl)-2-[(1R,2S)-2-fluoro-1-cyclopropyl)amino]methylene-3-oxopropionate was dissolved in 50ml of N,N-dimethylformamide and 0.9g of sodium fluoride (NaF) was added thereto. This mixture was refluxed for 4 hours and cooled down to normal temperature and then poured into 200ml of water. The produced solid was filtered, washed with water and air dried to obtain 4.2g (Yield: 90%) of the desired compound.

mp. 175-179°C

$[\alpha]_D^{20}$ = -46° (C 1.00, $CHCl_3$)

^1H NMR ($CDCl_3$): δ 1.40(t,3H), 1.2-1.9(m,2H), 4.02(m,1H), 4.4(m,2.5H), 5.26(m,0.5H), 8.21(t,1H), 8.56(s,1H)

Step (3): Synthesis of 8-chloro-6,7-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylate;

2.35g of ethyl 8-chloro-6,7-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylate was added to a mixture of 25ml of glacial acetic acid, 11ml of water and 1.8ml of concentrated sulfuric acid and the whole mixture was refluxed for 1.5 hours. The reaction solution was cooled down to room temperature and poured into 30ml of ice water. The produced solid was filtered, washed with water and air dried to obtain 2.13g (Yield: 99%) of the title compound as a white crystal.

mp. 180-181°C

$[\alpha]_D^{20}$ = -35.0° (C 1.00, $CHCl_3$)

^1H NMR ($CDCl_3$): δ 1.3-2.0(m,2H), 4.20(m,1H), 4.51(m,0.5H), 5.30(m,0.5H), 8.28(t,1H), 8.89(s,1H)

Preparation 36

Synthesis of 6,7,8-trifluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline carboxylic acid

4.56g (Yield: 80%) of the title compound was prepared according to the same procedure as Preparation 35 from 5g of ethyl 3-(2,3,4,5-tetrafluorophenyl)-3-oxopropionate.

mp. 188-190°C

$[\alpha]_D^{20}$ = -10° (C 1.00, MeOH)

^{1}H NMR ($CDCl_3$): δ 1.65(m,1H), 1.90(m,1H), 3.95(m,1H), 4.56(m,0.5H), 5.32(m,0.5H), 8.10(m,1H), 8.81(s,1H)

Preparation 37

Synthesis of 5-amino-6,7,8-trifluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline carboxylic acid

6.27g (Yield: 65%) of the title compound was prepared according to the same procedure as Preparation 35 from 8.46g of ethyl 3-(2,3,4,5,6-pentafluorophenyl)-3-oxopropionate.

^{1}H NMR ($CDCl_3$): δ 1.95(t,3H), 1.1-2.0(m,2H), 3.80(m,1H), 4.50(m,0.5H), 5.23(m,0.5H), 6.75(bs,2H), 8.65(s,1H)

Preparation 38

Synthesis of 6,7-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

5.83g (Yield: 72%) of the title compound was prepared according to the same procedure as Preparation 35 from 7.2g of ethyl 3-(2,4,5-trifluoro-3-methoxyphenyl)-3-oxopropionate.

mp. 180°C (decomposed)

$[\alpha]_D^{20}$ = -9° (C 1.00, $CHCl_3$/MeOH = 1/1)

^1H NMR ($CDCl_3$-CD_3OD): δ 1.4-1.9(m,2H), 4.0(m,1H), 4.1(s,3H), 4.5(m,0.5H), 5.3(m,0.5H), 8.0(t,1H,J=10Hz), 8.8(s,1H)

Preparation 39

Synthesis of 7-chloro-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

0.72g (Yield: 62%) of the title compound was prepared according to the same procedure as Preparation 35 from 1g of ethyl 3-(2-chloro-3-fluoropyridin-5-yl)-3-oxopropionate.

^1H NMR (DMSO-d_6): δ 1.69(m,2H), 3.70(m,1H), 4.65(m,0.5H), 5.43(m,0.5H), 8.41(d,1H), 8.90(s,1H), 13.81(b,1H)

Example 1

Synthesis of 6,8-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-7-(6-methyl-3,6-diazabicyclo[3.1.0]hexan-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

0.10g of 6,7,8-trifluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 0.1g of 6-methyl-3,6-diazabicyclo[3.1.0]hexane were added to 3ml of pyridine and the whole mixture was reacted for 24 hours at 40°C. After removing the pyridine by distillation under reduced pressure, the residue was dispersed in 3ml of ethyl acetate. Then, the produced solid was filtered to obtain 0.060g (Yield: 48%) of the title compound.

mp. 200-203°C (decomposed)

^{1}H NMR ($CDCl_3$): δ 1.4-1.9(m,2H), 2.38(s,2H), 2.40(s,3H), 3.89(m,5H), 4.46(m,0.5H), 5.25(m,0.5H), 7.75(d,1H), 8.65(s,1H)
IR (KBr): 1457, 1518, 1622, 1732, 3457 cm^{-1}

Example 2
Synthesis of 7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6,8-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

0.10g of 6,7,8-trifluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 0.10g of 3,6-diazabicyclo[3.1.0]hexane were added to 3ml of pyridine and the mixture was reacted overnight at 45°C. After removing the pyridine by distillation under reduced pressure, the residue was dispersed in 3ml of methanol and filtered. Then, the filter cake was washed with 1ml of methanol and dried to obtain 0.08g (Yield: 66.7%) of the title compound.

mp. 224-226°C (decomposed)
$[\alpha]_D^{20}$ = +29.0° (C 1.00, $CHCl_3$/MeOH = 1.5/1.0, v/v)
^{1}H NMR ($CDCl_3$+CD_3CO_2D): δ 1.4-1.9(m,2H), 3.00(s,2H), 3.90(m,5H), 4.50(m,0.5H), 5.30(m,0.5H), 8.02(d,1H), 8.72(s,1H)
IR (KBr): 1411, 1458, 1520, 1620, 1728, 3445 cm^{-1}

Example 3
Synthesis of 6,8-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-7-(1-methyl-3,6-diazabicyclo[3.1.0]hexan-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

0.10g of 6,7,8-trifluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 0.10g of 1-methyl-3,6-diazabicyclo[3.1.0]hexane were added to 4ml of pyridine and the mixture was reacted for two days at 40°C. After removing the pyridine by distilla-

tion under reduced pressure, the residue was dispersed in 3ml of methanol and filtered. The filter cake was washed with 1ml of methanol and dried to obtain 0.06g (Yield: 48%) of the title compound.

mp. 210-212°C (decomposed)

^{1}H NMR ($CDCl_3$): δ 1.50(s,3H), 1.4-1.9(m,2H), 4.00(m,5H), 4.50(m,0.5H), 5.29(m,0.5H), 7.80(d,1H), 8.70(s,1H)

IR (KBr): 1410, 1461, 1622, 1727, 3445 cm^{-1}

Example 4

Synthesis of 5-amino-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6,8-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

0.05g of 5-amino-6,7,8-trifluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 0.05g of 3,6-diazabicyclo[3.1.0]hexane were added to 5ml of pyridine and the mixture was reacted for one day at 45°C. After removing the pyridine by distillation under reduced pressure, the residue was dispersed in 5ml of ethyl acetate and the produced solid was filtered. The solid was dissolved in 2ml of chloroform-methanol (5:2 by volume) and then 3ml of ethyl acetate was added thereto. The produced crystal was filtered and dried to obtain 0.02g (Yield: 33%) of the title compound as a yellow crystal.

mp. 226-228°C (decomposed)

^{1}H NMR ($CDCl_3$+CD_3OD): δ 1.3-1.9(bm,2H), 2.75(s,2H), 3.81(q,4H), 4.30(m,1H), 4.46(m,0.5H), 5.29(m,0.5H), 8.54(s,1H)

IR (KBr): 1439, 1515, 1634, 1710, 3423 cm^{-1}

Example 5

Synthesis of 8-chloro-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-7-(1-methyl-3,6-diazabicyclo[3.1.0]hexan-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

0.10g of 8-chloro-6,7-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 0.09g of 1-methyl-3,6-diazabicyclo[3.1.0]hexane were added to 5ml of pyridine and the resulting mixture was reacted overnight at 45°C. The pyridine was removed by distillation under reduced pressure and the residue was dispersed in 5ml of absolute ethanol. The produced crystal was filtered and then dried to obtain 0.05g (Yield: 40%) of the title compound.

mp. 185-186°C (decomposed)

^{1}H NMR ($CDCl_3$): δ 1.1-1.8(m,2H), 1.47(s,3H), 3.65(m,5H), 4.17(m,1H), 4.50(m,0.5H), 5.28(m,0.5H), 8.00(d,1H), 8.79(s,1H)

IR (KBr): 1447, 1613, 1728, 3450 cm^{-1}

Example 6

Synthesis of 8-chloro-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

0.32g of 8-chloro-6,7-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was added to 5ml of acetic anhydride and to this solution was added 0.07g of boric acid. Then, the whole mixture was reacted for 15 minutes at 90°C and the acetic anhydride was removed by distillation under reduced pressure. The residue was dispersed in 10ml of isopropylether and filtered to obtain 0.42g of boric acid complex compound. This complex compound and 0.20g of 3,6-diazabicyclo[3.1.0]hexane were added to 9.4ml of pyridine and the resulting mixture was reacted for 24 hours at

normal temperature. The produced crystal was filtered, dispersed in 5ml of methanol and stirred for 10 minutes. Then, the resulting solution was filtered again and dried to obtain 0.16g (Yield: 44%) of the title compound.

mp. 223-224°C (decomposed)

$[\alpha]_D^{20}$ = -106° (C 1.10, $CHCl_3$/MeOH = 4/1, v/v)

^1H NMR ($CDCl_3$+CD_3COOD): δ 1.1-1.9(m,2H), 2.74(s,2H), 3.74(m,4H), 4.24(m,1H), 4.56(m,0.5H), 5.34(m,0.5H), 7.98(d,1H), 8.80(s,1H)

IR (KBr): 1448, 1499, 1614, 1724 cm^{-1}

Example 7

Synthesis of 8-chloro-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-(cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

0.16g (Yield: 44%) of the title compound was prepared according to the same procedure as Example 6 except that 0.32g of 8-chloro-6,7-difluoro-1-(cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid is used instead of 8-chloro-6,7-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

^1H NMR ($CDCl_3$+CD_3COOD): δ 1.1-1.9(m,2H), 2.74(s,2H), 3.74(m,4H), 4.24(m,1H), 4.56(m,0.5H), 5.34(m,0.5H), 7.98(d,1H), 8.80(s,1H)

IR (KBr): 1448, 1499, 1614, 1724 cm^{-1}

Example 8

Synthesis of 7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6,8-difluoro-1-(cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

0.08g (Yield: 66.7%) of the title compound was prepared according to the same procedure as Example 2 except that 0.1g of 6,7,8-trifluoro-1-(cis-2-fluoro-1-cyclopro-

pyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid is used instead of 6,7,8-trifluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

mp. 270-272°C (decomposed)

^{1}H NMR ($CDCl_3$+CD_3COOD): δ 1.4-1.9(m,2H), 3.00(s,2H), 3.90(m,5H), 4.50(m,0.5H), 5.30(m,0.5H), 8.02(d,1H), 8.72(s,1H)

IR (KBr): 1411, 1458, 1520, 1620, 1728, 3445 cm^{-1}

Example 9

Synthesis of 7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-(cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

0.06g (Yield: 48.8%) of the title compound was prepared according to the same procedure as Example 2 except that 0.1g of 6,7-difluoro-1-(cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid is used instead of 6,7,8-trifluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

mp. 247-249°C (decomposed)

^{1}H NMR ($CDCl_3$+CD_3OD+CD_3COOD): δ 1.4-1.9(m,2H), 2.90(s,2H), 3.80(q,4H), 4.17(m,1H), 4.50(m,0.5H), 5.30(m,0.5H), 7.02(d,1H), 7.80(d,1H), 8.51(s,1H)

IR (KBr):1413, 1457, 1521, 1624, 1725, 3270, 3442 cm^{-1}

Example 10

Synthesis of 5-amino-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6,8-difluoro-1-(cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

0.02g (Yield: 33%) of the title compound was prepared according to the same procedure as Example 4 except that 0.05g of 5-amino-6,7,8-trifluoro-1-(cis-2-fluoro-1-cyclo-

propyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid is used instead of 5-amino-6,7,8-trifluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

mp. 249-251°C (decomposed)

^{1}H NMR ($CDCl_3$+CD_3OD): δ 1.3-1.9(bm,2H), 2.75(s,2H), 3.81(q,4H), 4.30(m,1H), 4.46(m,0.5H), 5.29(m,0.5H), 8.54(s,1H)

IR (KBr):1439, 1515, 1634, 1710, 3423 cm^{-1}

Example 11

Synthesis of 7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

0.9g of boric acid was added to 40ml of acetic anhydride and this mixture was dissolved thoroughly under heating at 80°C. After cooling down to normal temperature, 3.2g of 6,7-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was added to the solution, which was then stirred for 30 minutes. Excessive amount of acetic anhydride was removed by distillation and the residue was dispersed in isopropylether and then filtered to obtain white crystalline solid. This solid was reacted with 2.6g of 3,6-diazabicyclo[3.1.0]hexane in 30ml of pyridine for one day at normal temperature. The solvent was removed by distillation under reduced pressure and the residue was dispersed in 10ml of methanol-ethanol (1:1 by volume). Then, 2ml of concentrated hydrochloric acid was added dropwise slowly to this solution in order to dissolve thoroughly. 4ml of triethylamine was added dropwise to the thus obtained solution and the resulting solution was filtered to obtain 2.0g (Yield: 51.9%) of the title compound as a pale yellow solid.

mp. 220°C (decomposed)

^{1}H NMR ($CDCl_3$+acetic acid-d_4): δ 8.8(s,1H), 7.8(d,1H), 5.2(m,0.5H), 4.4(m,0.5H), 3.8(m,5H), 3.6(s,3H), 3.1(s,2H), 1.5(m,2H)

$[\alpha]_D^{20}$ = +4° (C 1.00, $CHCl_3$)

Example 12

Synthesis of 7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

0.1g of 7-chloro-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and 0.1g of 3,6-diazabicyclo[3.1.0]hexane were reacted in 2ml of pyridine for 2 hours at normal temperature. The produced crystal was filtered and washed with 2ml of methanol to obtain 0.08g (Yield: 70%) of the title compound.

mp. 240°C (decomposed)

^{1}H NMR ($CDCl_3$+CD_3OD): δ 1.4-1.9(m,2H), 3.0(s,2H), 3.7(m,1H), 3.8(d,1H,J=12Hz), 4.3(d,1H, J=12Hz), 4.6(m,0.5H), 5.4(m,0.5H), 8.0(d,1H,J=12Hz), 8.7(s,1H)

Example 13

Synthesis of 8-chloro-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid lactate

100mg of 8-chloro-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was dissolved in a mixture of chloroform and methanol and then 0.022ml of 90% lactic acid was added thereto. This solution was stirred for 3 hours at normal temperature and distilled under reduced pressure and then crystallized from ether. The

produced crystal was filtered and dried to obtain 115mg (Yield: 92.7%) of the title compound having pale yellow colour.

mp. 178-180°C (decomposed)

^{1}H NMR ($CDCl_3$+CD_3OD): δ 1.0-1.8(m,5H), 3.7(m,6H), 4.2(m,2H), 4.5(m,0.5H), 5.3(m,0.5H), 8.0(d,1H), 8.8(s,1H)

Example 14

Synthesis of 8-chloro-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid methane sulfonate

100mg of 8-chloro-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was dissolved in a mixed solvent of chloroform and methanol and then 0.027ml of 70% methane sulfonic acid was added thereto. This solution was stirred for one hour at normal temperature and distilled under reduced pressure and then crystallized from ether. The produced crystal was filtered and dried to obtain 120mg (Yield: 96%) of the title compound having pale yellow colour.

mp. 220°C (decomposed)

^{1}H NMR ($CDCl_3$+CD_3OD): δ 1.1-1.8(m,2H), 2.7(s,3H), 3.65(m,6H), 4.18(m,1H), 4.5(m,0.5H), 5.27(m,0.5H), 8.0(d,1H), 8.8(s,1H)

Example 15

Synthesis of 8-chloro-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride

50mg of 8-chloro-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-

dihydroquinoline-3-carboxylic acid was dissolved in a mixture of chloroform and methanol and then 1ml of 2N-hydrochloric acid/methanol was added thereto. This solution was stirred for 30 minutes at room temperature and distilled under reduced pressure and then crystallized from ether. The produced crystal was filtered and dried to obtain 52mg (Yield: 93%) of the title compound having pale yellow colour.

mp. 218-220°C (decomposed)

^{1}H NMR ($CDCl_3$+CD_3OD): δ 1.1-1.8(m,2H), 3.65(m,6H), 4.17(m,1H), 4.47(m,0.5H), 5.27(m,0.5H), 8.0(d,1H), 8.78(s,1H)

Example 16

Synthesis of 7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6,8-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride

1.0g of 7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6,8-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was added to 7ml of methanol and then 2.7ml of 2N-hydrochloric acid was added thereto while the whole mixture was cooled down under ice water. After stirring this solution for about one hour at the same temperature, the produced crystal was filtered and dried to obtain 1.0g (Yield: 91%) of the title compound.

mp. 220°C (decomposed)

^{1}H NMR (D_2O+DSS+DCl): δ 1.7(m,2H), 4.1(s,2H), 4.2(m,4H), 4.8(m,0.5H), 5.5(m,0.5H), 7.3(d,1H), 8.6(s,1H)

$[\alpha]_D^{20}$ = -13° (C 1.00, H_2O)

The following examples 17 to 22 relate to the preparation of antibacterial composition which contain the quino-

line based compound according to the present invention as an active ingredient.

Example 17

The compound prepared in Example 2	25g
Starch	5g
Lactose	3.5g
Talc	1.5g

The above components were mixed with ethanol and granulated according to the conventional method and then filled into 100 capsules.

Example 18

The compound prepared in Example 6	25g
Starch	5g
Lactose	3.5g
Talc	1.5g

The above components were mixed with ethanol and granulated according to the conventional method and then filled into 100 capsules.

Example 19

The compound prepared in Example 2	25g
Starch	5.4g
Calcium carboxymethyl cellulose	4.0g
Microcrystalline cellulose	5.0g
Magnesium stearate	0.6g

The above components were mixed with ethanol and granulated according to the conventional method and then compressed into 100 tablets.

Example 20

The compound prepared in Example 6	25g
Starch	5.4g
Calcium carboxymethyl cellulose	4.0g
Microcrystalline cellulose	5.0g
Magnesium stearate	0.6g

The above components were mixed with ethanol and granulated according to the conventional method and then compressed into 100 tablets.

Example 21

The compound prepared in Example 2	0.5g
Lactic acid	1.2g

The above components were dissolved in 100ml of distilled water and the resulting solution was adjusted with aqueous NaOH solution to about pH 4 and then filled into 10 ampoules(10ml).

Example 22

The compound prepared in Example 6	0.5g
Lactic acid	1.2g

The above components were dissolved in 100ml of distilled water and the resulting solution was adjusted with aqueous NaOH solution to about pH 4 and then filled into 10 ampoules(10ml).

Biological Example 1
In vitro antibacterial activity test

The antibacterial activity of the compounds according to the present invention was evaluated by measuring their

minimum inhibitory concentration(MIC; μg/ml) against strains according to the agar plate dilution method(see: Chemotheraphy, 29(1), p76-79, 1981).

The overnight culture of the pathogenic strain(10^6 cells/ml) was inoculated to Mueller-Hinton agar so that each spot contained about 10^4 colony forming particles. After the agar was cultured for 18 hours at 37°C, the minimum concentration at which the test compounds could inhibit the apparent growth of the strains was determined as the minimum inhibitory concentration(MIC, μg/ml).

In this test, the ciprofloxacin was used as the control agents and the measured results as to the MIC of the compounds according to the present invention are described in the following Table 1. And subsequently, the antibacterial activities against methicillin resistant Staphylococcus aureus (MRSA) and ofloxacin resistant strain were described in Tables 2 and 3.

As a result, the compounds according to the present invention show an excellent antibacterial activity against resistant strains which cause great problems recently as well as against broad range of gram-positive and gram-negative strains.

Test Strains

1. Streptococcus pyogenes 308A
2. Streptococcus pyogenes 77A
3. Streptococcus faecium MD 86
4. Staphylococcus aureus SG 511
5. Staphylococcus aureus 285
6. Staphylococcus aureus 503
7. Escherichia coli 055
8. Escherichia coli DC 0
9. Escherichia coli DC 2

10. Escherichia coli TEM
11. Escherichia coli 1507E
12. Pseudomonas aeruginosa 9027
13. Pseudomonas aeruginosa 1592 E
14. Pseudomonas aeruginosa 1771
15. Pseudomonas aeruginosa 1771 M
16. Salmonella typhimurium
17. Klebsiella oxytoca 1082 E
18. Klebsiella aerogenes 1522 E
19. Enterobacter cloacae P99
20. Enterobacter cloacae 1321 E

Table 1. MIC determined by agar dilution test (μg/ml)

Test Strains	Compound						
	EX.1	EX.2	EX.3	EX.4	EX.5	EX.6	CFLX
1	0.781	0.195	0.195	0.391	0.098	0.098	3.125
2	0.781	0.195	0.195	0.195	0.098	0.098	0.781
3	0.391	0.098	0.195	0.098	0.098	0.049	0.781
4	0.049	0.013	0.025	0.007	0.007	0.007	0.195
5	0.049	0.025	0.025	0.013	0.013	0.013	0.391
6	0.049	0.013	0.025	0.013	0.013	0.013	0.391
7	0.013	≤0.004	0.007	≤0.004	0.007	≤0.004	0.007
8	0.391	0.098	0.195	0.195	0.098	0.098	0.391

Table 1. (continued)

Test Strains	Compound						
	EX.1	EX.2	EX.3	EX.4	EX.5	EX.6	CFLX
9	0.049	0.013	0.025	0.025	0.013	0.013	0.098
10	0.049	0.013	0.025	0.013	0.013	0.013	0.013
11	0.049	0.013	0.025	0.013	0.025	0.013	0.013
12	1.563	0.391	0.781	0.781	0.781	0.391	0.391
13	1.563	0.391	0.391	0.391	0.391	0.195	0.195
14	1.563	0.391	0.781	0.781	0.781	0.391	0.391
15	0.391	0.098	0.195	0.098	0.098	0.098	0.195
16	0.025	0.007	0.013	0.007	0.013	0.007	0.013
17	≤0.004	≤0.004	≤0.004	≤0.004	≤0.004	≤0.004	≤0.004
18	0.049	0.013	0.025	0.025	0.025	0.013	0.025
19	0.025	0.007	0.013	≤0.004	0.013	0.007	0.013
20	0.013	0.007	0.013	0.007	0.007	0.007	0.013

note) CFLX = Ciprofloxacin

Table 1. (continued)

Test Strains	Compound						
	EX.7	EX.8	EX.9	EX.10	EX.11	EX.12	CFLX
1	0.195	0.195	0.781	0.391	0.781	0.781	3.125
2	0.195	0.195	0.781	0.391	0.195	0.781	0.781
3	0.098	0.195	0.391	0.195	0.195	0.781	0.781
4	0.013	0.025	0.049	0.013	0.013	0.013	0.195
5	0.025	0.025	0.049	0.013	0.025	0.013	0.391
6	0.013	0.025	0.049	0.013	0.025	0.013	0.391
7	≤0.004	≤0.004	0.013	≤0.004	0.013	≤0.004	0.007
8	0.195	0.195	0.781	0.195	0.391	0.391	0.391
9	0.025	0.025	0.049	0.049	0.049	0.013	0.098
10	0.025	0.025	0.049	0.049	0.025	0.025	0.013
11	0.025	0.025	0.049	0.049	0.049	0.025	0.013
12	0.391	0.781	1.563	0.781	0.781	0.781	0.391
13	0.391	0.391	0.781	0.391	0.781	0.391	0.195
14	0.391	0.781	1.563	0.781	0.781	0.391	0.391
15	0.195	0.195	0.391	0.195	0.781	0.025	0.195

Table 1. (continued)

Test Strains	Compound						
	EX.7	EX.8	EX.9	EX.10	EX.11	EX.12	CFLX
16	0.013	0.013	0.025	0.007	0.013	0.013	0.013
17	≤0.004	≤0.004	≤0.004	≤0.004	≤0.004	≤0.004	≤0.004
18	0.025	0.025	0.098	0.049	0.049	0.025	0.025
19	0.013	0.013	0.025	0.007	0.025	0.013	0.013
20	0.013	0.007	0.013	0.007	0.007	0.007	0.013

Table 2. Antibacterial activity against MRSA, MIC (μg/ml)

Methicillin Resistant Staphylococcus aureus		CFLX	* CI-960	EX.6
1	MRSA 88 E	0.390	0.025	≤0.004
2	MRSA 121 E	0.390	0.025	≤0.004
3	MRSA 208 E	0.390	0.025	≤0.004
4	MRSA 256 E	0.390	0.025	≤0.004
5	MRSA 690 E	0.195	0.013	≤0.004
6	MRSA 692 E	0.195	0.013	≤0.004
7	MRSA 693 E	0.195	0.013	≤0.004
8	MRSA 694 E	0.195	0.013	≤0.004
9	MRSA 695 E	0.195	0.013	≤0.004
10	MRSA 697 E	0.195	0.013	≤0.004
11	MRSA 701 E	0.195	0.013	≤0.004

Table 2. (continued)

Methicillin Resistant Staphylococcus aureus		CFLX	* CI-960	EX.6
12	MRSA 703 E	0.195	0.013	≤0.004
13	MRSA 705 E	0.390	0.025	≤0.004
14	MRSA 706 E	0.195	0.013	≤0.004
15	MRSA 707 E	0.390	0.025	≤0.004
16	MRSA 708 E	0.195	0.025	≤0.004
17	MRSA 711 E	0.195	0.013	≤0.004
18	MRSA 714 E	0.195	0.013	≤0.004
19	MRSA 725 E	0.195	0.013	≤0.004

*CI-960

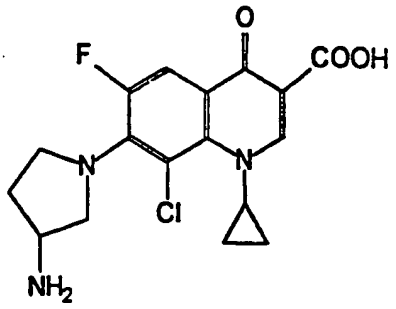


Table 3. Antibacterial activity against MRSA, MIC (μg/ml)

	Ofloxacin Resistant Strain		OFLX	EX.2	EX.6
1	Staphylococcus aureus	179	12.50	0.390	0.195
2	Staphylococcus aureus	241	12.50	0.780	0.195
3	Staphylococcus aureus	293	12.50	0.390	0.195
4	Staphylococcus aureus	303	6.250	0.390	0.195
5	Staphylococcus aureus	17613	25.00	0.780	0.195
6	Staphylococcus aureus	17740	≥50.00	1.563	0.390
7	Staphylococcus aureus	17746	12.50	0.390	0.195
8	Staphylococcus aureus	17845	6.250	0.390	0.195
9	Staphylococcus aureus	8236	12.50	0.390	0.195
10	Staphylococcus epidermidis	178	≥50.00	0.780	0.390
11	Staphylococcus epidermidis	291	≥50.00	0.780	0.390
12	Staphylococcus epidermidis	31989	≥50.00	1.563	0.390
13	Staphylococcus epidermidis	32965	≥50.00	0.780	0.390
14	Staphylococcus species	245	≥50.00	1.563	0.390
15	Enterococcus munchen		6.250	1.563	0.780

Table 3. (continued)

Ofloxacin Resistant Strain			OFLX	EX.2	EX.6
16	Enterococcus munchen	21777	6.250	1.563	0.780
17	Enterococcus knothe	101	3.125	0.390	0.390
18	Enterococcus D	30	3.125	0.390	0.390
19	Acinetobacter species	J 178	6.250	1.563	0.780
20	Acinetobacter species	J 180	6.250	1.563	0.780
21	Pseudomonas aeruginosa	55	12.50	12.50	6.250
22	Pseudomonas aeruginosa	60	3.125	0.780	0.390
23	Pseudomonas aeruginosa	91	25.00	12.50	6.250
24	Pseudomonasaeruginosa	1912261025	25.00	12.50	6.250
25	Pseudomonas aeruginosa	27911	12.50	12.50	6.250
26	Pseudomonas aeruginosa	30973	25.00	12.50	6.250
27	Pseudomonas aeruginosa	13-32-3	3.125	1.563	0.780
28	Pseudomonas aeruginosa	13-32-2	25.00	12.50	6.250
29	Pseudomonas aeruginosa	8-18-3	6.250	0.780	0.390
30	Pseudomonas aeruginosa	36-5-1	25.00	12.50	6.250

Table 3. (continued)

Ofloxacin Resistant Strain			OFLX	EX.2	EX.6
31	Pseudomonas aeruginosa	10-1-2	3.125	1.563	0.780
32	Klebsiella species	31660	0.098	0.025	0.025
33	Klebsiella species	30-30	3.125	0.390	0.390
34	Klebsiella species	30-92	3.125	1.563	0.780
35	Serratia species knothe	alt 2	3.125	1.563	0.780
36	Serratia species knothe	alt 5	6.250	1.563	0.780
37	Serratia species knothe	alt 9	1.563	0.390	0.390
38	Serratia species knothe	alt 10	1.563	0.390	0.390
39	Serratia species knothe	Y 39	6.250	0.780	0.780
40	Serratia species knothe	Y 42	3.125	0.390	0.390

Note: OFLX = Ofloxacin

Biological Example 2
bioavailability test

The bioavailability of the compound according to the present invention was determined using ICR mouse weighing about 30g. Specifically, the test compounds of the present invention were orally administered in an amount of 40mg/kg of body weight to 4 test animals and also adminis-

tered via subcutaneous injection in an amount of 40mg/kg to another 4 test animals, respectively. After administration, the blood concentration, half life($T_{1/2}$) and AUC (area under the curve) were measured at certain intervals and the bioavailability was calculated therefrom.

The obtained test results as to bioavailability are described in the following Table 4. As can be seen from the results, some compounds exhibit superior bioavailabilites in contrast to the control agent.

Table 4. Bioavailability of the compounds according to the present invention

Comp.	CFLX	EX.2	EX.4	EX.6	EX.11
F(%)	32.7	74.1	77.2	27.6	30.8

Note: CFLX = Ciprofloxacin
F = Bioavailability

Biological Example 3

antiinflammatory effect

To determine the antiinflammatory effect of the compounds according to the present invention, the test mouse (ICR mouse, 5 weeks old, 25-29g) was infected peritoneally with pathogenic strains and then the compounds prepared in the above Examples were administered. The results are represented as PD_{50}.

As can be seen from the results in the following Table 5, the compounds according to the present invention have more excellent antiinflammatory effect than the ciprofloxacin used as a control drug.

Table 5. PD_{50}(mg/kg) against the infected mouse

Pathogenic Strains		EX.2		EX.8		CFLX	
		Oral	S.I.	Oral	S.I.	Oral	S.I.
Streptococcus pyogenes	A77	42.58	20.80	≥50	≥25	>100	>50
Escherichia coli	078	0.90	0.33	2.68	0.58	1.67	0.21
Pseudomonas aeruginosa	771M	6.58	4.23	19.38	9.38	3.00	1.05
Staphylococcus aureus georgio		8.84	4.12	≥25	10.5	>100	>50

Biological Example 4

distribution of the administered compound in living tissues

The test results as to the distribution of the compounds in living tissues were determined against male ICR mouse. Specifically, the compound according to the present invention (the compound prepared in Example 2) and ciprofloxacin and ofloxacin were tested. They were orally administered in an amount of 40mg/kg of body weight to test animals and then the distributions at each tissue were determined. The results are described in the following Table 6.

As a result, it can be recognized that the compounds according to the present invention are existed in almost every living tissue with a still higher concentration in contrast to the control compounds.

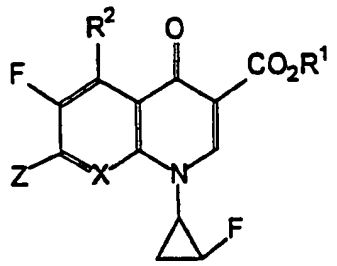
Table 6. Distribution in living tissues

	EX.2	CFLX	OFLX
Time(h)	1.5	1.5	1.5
Test animal No.	4	4	4
Heart	18.08±2.46	1.04±0.16	0.75±0.09
Lung	14.15±2.44	1.21±0.06	0.72±0.14
Liver	17.97±4.09	2.49±0.31	2.46±1.00
Salivary gland	8.35±1.61	1.12±0.13	0.62±0.07
Muscle	6.18±0.99	1.10±0.19	0.76±0.12
Kidney	15.03±2.61	2.12±0.39	1.30±0.22
Brain	0.50±0.07	0.02±0.00	0.07±0.01
Blood	6.71±0.54	0.47±0.01	0.82±0.13

Although this invention has been described in its preferred form with a certain degree of particularity, it is appreciated by those skilled in the art that the present disclosure of the preferred form has been made only by way of example and that numerous changes in the details of the contruction, combination and arrangement of parts may be resorted to without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS :

1. A quinoline compound represented by the following formula (I) :



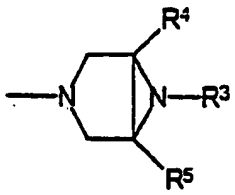
(I)

and its pharmaceutically acceptable salt, in which

R^1 represents hydrogen or ester forming group;

R^2 represents hydrogen, amino, lower alkylamino, hydroxy, lower alkoxy, mercapto, lower alkylthio or halogen;

Z represents an amine compound having the following formula :



(wherein, R^3 represents hydrogen or lower alkyl; R^4 and R^5 are identical to or different from each other, and independently represent hydrogen or C_1-C_2 alkyl); and

X represents N or C-R^6 (wherein, R^6 represents hydrogen, halogen, hydroxy, methyl, cyano, nitro or methoxy).

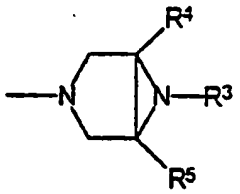
2. The compound of claim 1, wherein

R^1 represents hydrogen;

R^2 represents hydrogen or amino;

Z represents an amine compound having the following

formula :



(wherein, R^3 represents hydrogen or lower alkyl; R^4 and R^5 are identical to or different from each other, and independently represent hydrogen or C_1-C_2 alkyl);

X represents N or C-R^6 (wherein, R^6 represents hydrogen, halogen or methoxy).

3. The compound of claim 2, wherein the compound is (1) 6,8-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-7-(6-methyl-3,6-diazabicyclo[3.1.0]hexan-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof; (2) 7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6,8-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof; (3) 6,8-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-7-(1-methyl-3,6-diazabicyclo[3.1.0]hexan-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof; (4) 5-amino-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6,8-difluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof; (5) 8-chloro-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-7-(1-methyl-3,6-diazabicyclo[3.1.0]hexan-3-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof; (6) 8-chloro-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof; (7) 8-chloro-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-(cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;

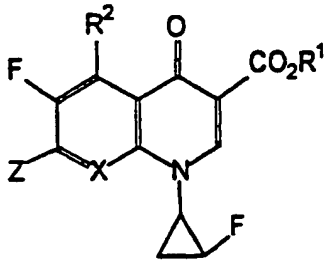
(8) 7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6,8-difluoro-1-(cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;
(9) 7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-(cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;
(10)5-amino-7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6,8-difluoro-1-(cis-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof;
(11)7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and the salt thereof or; (12) 7-(3,6-diazabicyclo[3.1.0]hexan-3-yl)-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and the salt thereof.

4. The compound according to claim 1, wherein the ester forming group is lower alkyl, C_3-C_7 cycloalkyl or benzyl.

5. The compound according to claim 1, wherein the pharmaceutically acceptable salt is acid addition salt.

6. The compound according to claim 5, wherein the acid addition salt is selected from the group consisting of lactate, methane sulfonate and hydrochloride.

7. A process for preparing a quinoline compound having the following formula (I),



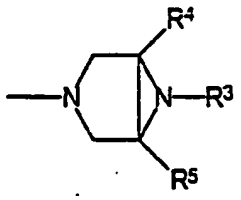
(I)

and its pharmaceutically acceptable salt, in which

R^1 represents hydrogen or ester forming group;

R^2 represents hydrogen, amino, lower alkylamino, hydroxy, lower alkoxy, mercapto, lower alkylthio or halogen;

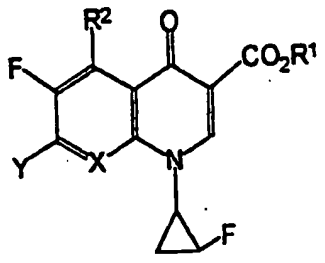
Z represents an amine compound having the following formula :



(wherein, R^3 represents hydrogen or lower alkyl; R^4 and R^5 are identical to or different from each other, and independently represent hydrogen or C_1-C_2 alkyl); and

X represents N or C-R^6 (wherein, R^6 represents hydrogen, halogen, hydroxy, methyl, cyano, nitro or methoxy),

characterized in that a compound having the following formula (II) :



(II)

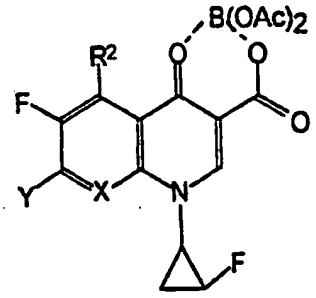
or its complex compound, in which R^1, R^2 and X are defined as above and Y represents a halogen, is reacted with a compound having the following formula (III) :

ZH (III)

wherein Z is defined as above, in the presence of a base.

8. The process according to claim 7, characterized in that said base is selected from the group consisting of sodium hydroxide, potassium hydroxide, triethylamine, pyridine, picoline, ruthidine, 1,4-diazabicyclo[2.2.2]-octane(DABCO), 1,8-diazabicyclo[5.4.0]-undec-7-ene(DBU), and 1,5-diazabicyclo[4.3.0]non-5-ene(DBN).

9. The process according to claim 7, characterized in that the complex compound of the compound of formula (II) is the boron complex compound represented by the following formula (II-1) :



(II-1)

in which,
R^1 and X are defined as in claim 7; and
Y represents a halogen.

10. An antibacterial composition characterized in that it comprises at least one of the compounds according to any one of claims 1 to 6 or pharmaceutically acceptable salt thereof as an active ingredient, together with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 95/00084

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 487/08, 471/04, 519/00, 215/56; A 61 K 31/47, 31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 487/08, 471/04, 519/00, 215/56; A 61 K 31/47, 31/435

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92/12 155 A1 (HANMI PHARMACEUTICAL CO., LTD.) 23 July 1992 (23.07.92), abstract; claims 1-5; page 23, lines 8-11.	1-8,10
A	EP 0 603 887 A2 (DAIICHI PHARMACEUTICAL CO.,LTD.) 29 June 1994 (29.06.94), abstract; claims 1,5,12; page 8, lines 3-43; page 7, lines 43-47.	1-8,10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 September 1995 (05.09.95)	13 September 1995 (13.09.95)

Name and mailing address of the ISA/ AT	Authorized officer
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Facsimile No. 1/53424/535	Telephone No. 1/5337058/33

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 95/00084

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
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